Total synthesis of new microbial sphingolipid-type signaling molecules

Dissertation

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- D. Braga, D. Last, M. Hasan, H. Guo, D. Leichnitz, Z. Uzum, I. Richter, F. Schalk, C. Beemelmanns, C. Hertweck, G. Lackner *ACS Chem. Biol.*, **2019**, *14*, 2088.
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Contents

List of abbreviations

DCC Dicyclohexylcarbodiimide

DIC Diisopropylcarbodiimide

HOBt 1-Hydroxybenzotriazole

HBTU 3-[Bis(dimethylamino)methyliumyl]-3*H*-benzotriazol-1-oxide hexafluorophosphate

HATU 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

COMU 1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate

EDC 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

TCNHPI Tetrachloro-*N*-hydroxyphthalimide

CITU Tetrachloro-*N*-hydroxyphthalimide tetramethyluronium hexafluorophosphate

DIPEA *N*,*N*-Diisopropylethylamine

NMM *N*-Methylmorpholine

4-DMAP 4-Dimethylaminopyridine

Tf_2O Trifluoromethanesulfonic anhydride

PPTS Pyridinium *p*-toluenesulfonate

DIBAL-H Diisobutylaluminium hydride

TMSOTf Trimethylsilyl trifluoromethanesulfonate

TBSOTf *tert*-Butyldimethylsilyl trifluoromethanesulfonate

TIPSOTf Triisopropylsilyl trifluoromethanesulfonate

BTMSA Bis(trimethylsilyl)acetylene

TBAF Tetra-*n*-butylammonium fluoride

TBAI Tetra-*n*-butylammonium iodide

HMPA Hexamethylphosphoric triamide

DMPU 1,3-Dimethyl-1,3-diazinan-2-one

LDA Lithium diisopropylamide

RuCl[TsDPEN](mesitylene) (Noyori's catalyst) [*N*-[2-(Amino-)-1,2-diphenylethyl]-(4-toluenesulfonyl)amidato]chloro[η^6-mesitylene]-ruthenium II

KHMDS Potassium bis(trimethylsilyl)amide

DIAD Diisopropyl azodicarboxylate

HG II (Hoveyda-Grubbs-catalyst 2nd generation) (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro(*o*-isopropoxyphenylmethylene)ruthenium II

Lawesson's reagent 2,4-Bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide

BHT 2,6-Di-*tert*-butyl-4-methylphenol

***m*-CPBA** 3-Chlorobenzene-1-carboperoxoic acid

NOESY Nuclear Overhauser Enhancement Spectroscopy

Piv Pivaloyl-

Cp Cyclopentadienyl-

Bt 1-Benzotriazolyl-

SPE solid-phase extraction

LC Liquid chromatography

HPLC High performance liquid chromatography

UPLC Ultra-high performance liquid chromatography

NMR Nuclear magnetic resonance

IR Infra-red

FT Fourier transformation

HRMS High-resolution mass spectrometry

ESI Electrospray ionization

TOF Time of flight

TBME *tert*-Butylmethylether

DMSO Dimethylsulfoxide

DMF *N*,*N*-Dimethylformamide

THF Tetrahydrofuran

TBS *tert*-Butyldimethylsilyl-

TIPS Triisopropylsilyl-

TBDPS *tert*-Butyldiphenylsilyl-

TES Triethylsilyl-

TFA Trifluoroacetic acid

1 Introduction

1.1 Sphingolipids and Sulfonolipids

1.1.1 Physiological role

Sphingolipids were originally discovered 1884 by J.L.W. Thudichum in a study of the human brain tissue.[1] Ever since then, they have been object of interest due to their widespread biological functions as integral part of cell membranes and as signaling molecules. Despite their simple chemical core structure, it took 70 years after their initial discovery to accomplish the first racemic total synthesis of sphingosine and another 15 years for the first enantioselective total synthesis.[2–5] Only then the structure was correctly identified and defined as consisting of a lipid backbone encompassed by a polar head group with a *N*-acylated 2-amino-1,3-diol moiety (figure 1.1A). Both, condensed fatty acid and alkyl chain can differ in hydroxylation and unsaturation[6,7] and the C-1 alcohol can be further modified, which allows for more diversification; phosphorylation yields the phosphonolipids, glycosylation yields the glycosphingolipids.[8]

The structural diversity of sphingolipids allows for mediating manifold biological functions, which include cell differentiation processes, cell growth and apoptosis, making them suitable synthetic targets for tumor treatment.[10,11] Furthermore, C-1 glycosylated sphingolipids play a role in cell-cell interactions,[12] a disorder in glycosphingolipids production is deemed responsible for several diseases, such as Gaucher disease, Fabry disease or Krabbe disease.[13] Sphingolipids constitute up to 10 % of all lipids of a typical mammalian cell, where they are mostly found in the outer membrane, often in lipid rafts with cholesterol.[14] A special class of hydroxylated sphingolipids is used to prevent the loss of water in the stratum corneum.[15,16] As such, they are of great interest for the cosmetic industry as well.[17]

Despite their great abundance in mammalian cells, bacterial sphingolipids have only been discovered in recent years thanks to the rapidly growing field of lipidomics.[18,19] So far, they are limited to only a handful of bacterial taxa, where they provide different functions: From modulation of host microbe interactions,[20] over bacterial life cycle and sporulation regulation[21] to microbial predation.[22]

A structurally similar class of lipids in bacterial cells are sulfonolipids, differing in the sulfono group at C-1 (figure 1.1B).[23] Interestingly, sulfonolipids have not been found in mammalian cells to date, which renders them excellent dietary markers for the bacteria in the human gut microbiome in metabolomic studies.[24,25] These lipids are also used for movement by bacteria of the *Cytophaga*-group, which glide with their sulfonolipid and ornithine rich membranes.[26,27] Mutants lacking the genes to produce sulfonolipids were also deprived of their moving ability,[28,29] however the sulfonolipid content and the gliding ability were restored upon addition of cysteate.[30]

In a chemical ecological context, sulfonolipids were found to induce multicellularity in certain choanoflagellates. These predatory eukaryotes not only represent the last phylogenetic branch of unicellular organisms before multicellular animals emerged,[31] some choanoflagellates, like *Salpingoeca rosetta*, have both solitary and multicellular stages in their life histories.[32] This offers the opportunity to study the evolution of multicellularity, which has been topic of debate for several decades. The multicellular form called rosette after its shape arises from several rounds of cell division, where sister cells do not completely separate.[33,34] This process is mediated by their bacterial prey, as evidenced by antibiotic treatment of

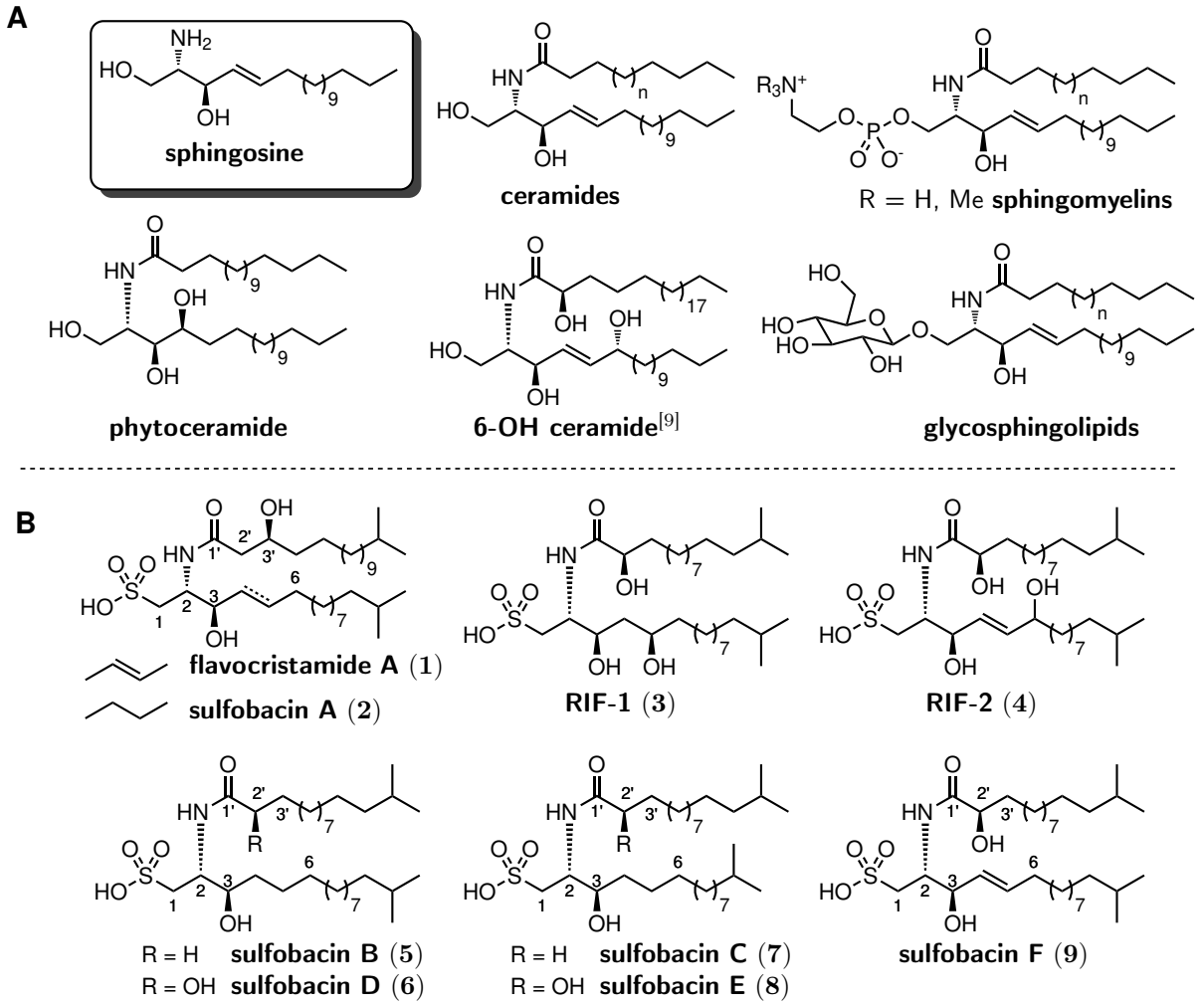


Figure 1.1: A) General structure of different sphingolipid classes; B) structures of selected sulfonolipids isolated from *A. machipongonensis*.

the wild type (figure 1.2). Lipid extraction of the inducing strain *Algoriphagus machipongonensis* revealed specific sulfonolipids named rosette inducing factors (**RIF**s) as responsible molecules (figure 1.2).[35,36] These were found to initiate cell division in a femtomolar range, but only up to 25 % of all cells were converted into the multicellular stage. Curiously, *A. machipongonensis* produces lysophosphatidyl ethanol amines (**LPE**s), which elicit no response on their own, but work synergistically with **RIF**s to further mature the colonies and increase their percentage to up to 82 % of all cells. Interestingly, the same strain produces an inhibitor of rosettes **IOR** (**10**), which reduces the amount of rosettes, up to zero, if only **RIF-2 4** is applied.[37]

It was also found, that members of the sulfonolipid family, sulfobacins A and B (**2** and **5**), show inhibitory activity against von Willebrand factor receptors, which play important roles in the formation of thromboses, or a DNA-polymerase on a micromolar range.[38] These studies exemplify that research only starts to understand the role and abundance of sulfonolipids.

1.1.2 Biosynthesis of sphingo- and sulfonolipids

To understand the biological availability of these lipids it is necessary to have detailed knowledge of their production in living cells. The biosynthesis of sphingolipids shares a multitude of steps across the different kingdoms of eukaryotes, yeast and bacteria and is overall best understood for mammals (scheme 1.1). As such, the mammalian *de novo*-biosynthesis starts by the condensation of serine with

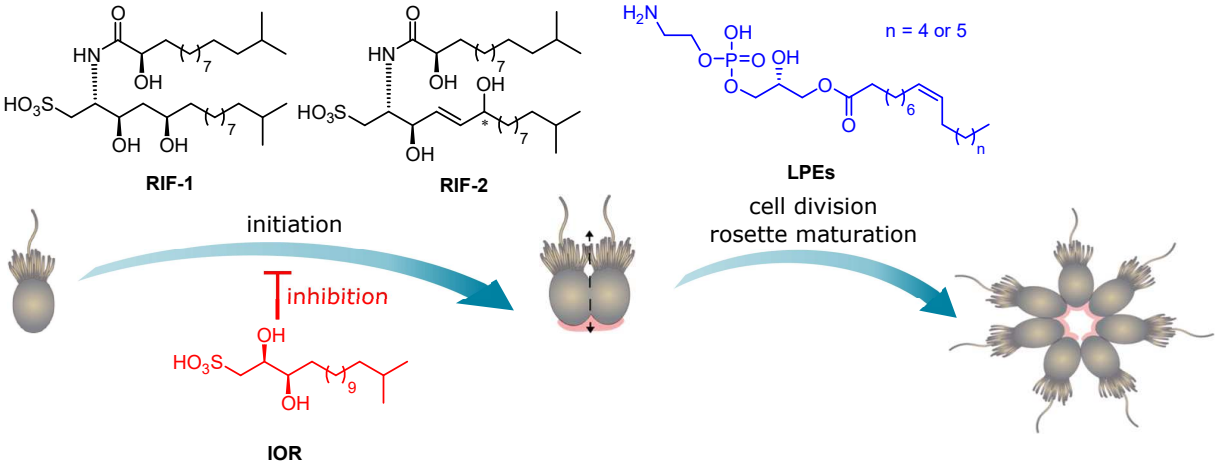
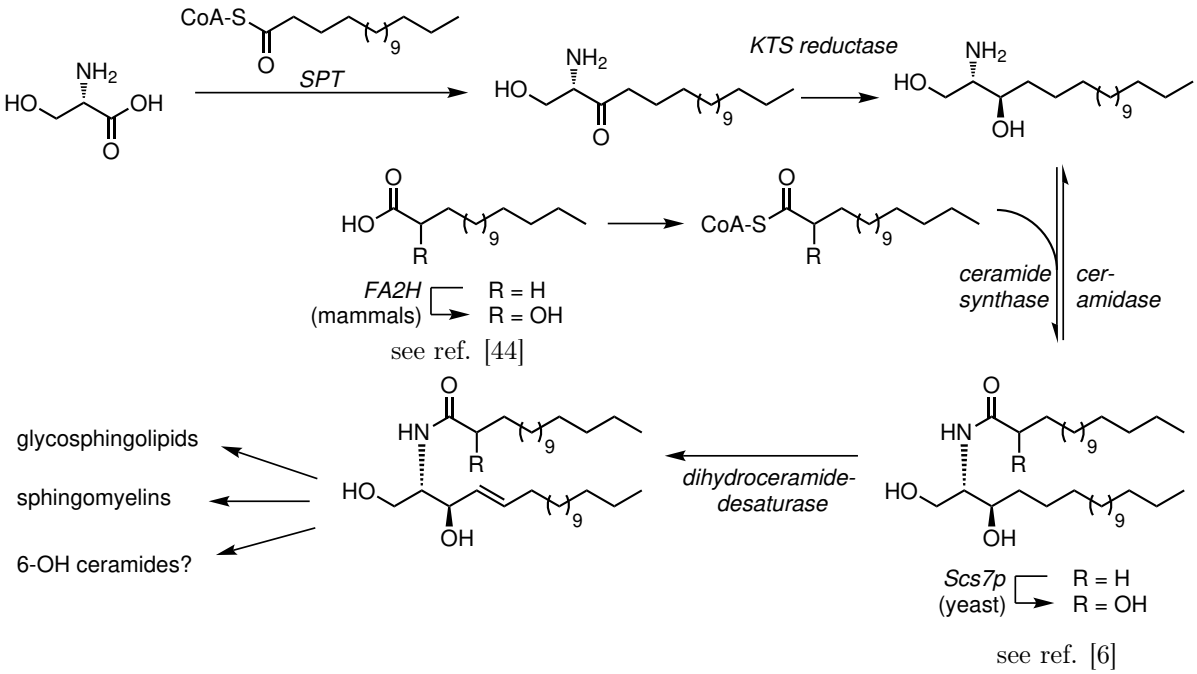


Figure 1.2: Influence of sulfonolipids on the life cycle of *S.rosetta*.

palmitoyl-CoA catalyzed by a serine palmitoyl transferase (SPT).[39–41] The so formed 3-keto-sphinganine is then enzymatically reduced and *N*-acylated through a ceramide synthase afterwards.[42] Desaturation by a dihydroceramide-desaturase forms the ceramide core structure and can be followed by further modifications to glycosphingolipids and sphingomyelins for example. To date the biosynthetic origin of sphingolipid hydroxylation at C-6 is unknown, however it may be speculated that an enzymatic allylic oxidation can be held accountable.[43]

Across the kingdoms, there are differences in the biosynthesis. Yeast cells for example install the hydroxy group after the amide bond has been formed in contrast to the use of hydroxylated fatty acids in mammals.[6,42,44] And for bacteria, recent reports indicate that the acylation takes place prior to the reduction of the 3-keto-sphinganine.[45]



Scheme 1.1: Biosynthesis of sphingolipids.

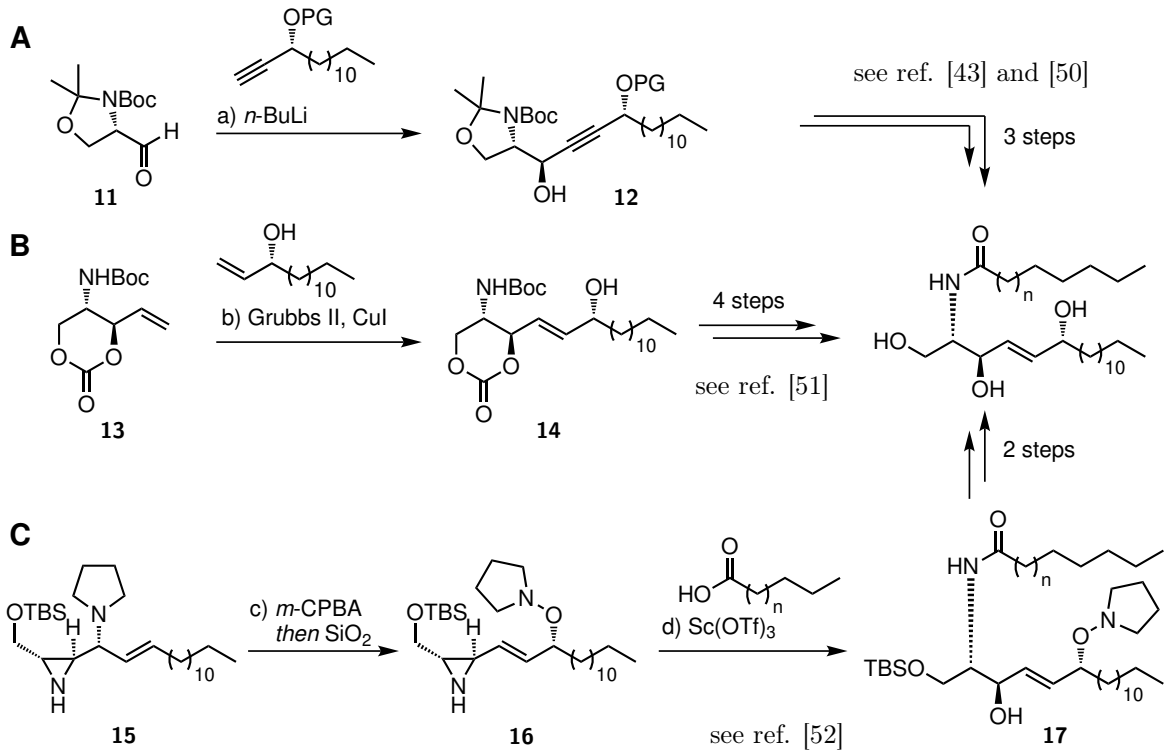
However, less is known about the biosynthesis of sulfonolipids; it is assumed to proceed in a similar fashion to the sphingolipid biosynthesis. Instead of serine, cysteic acid likely is used as starter amino acid for the SPT,[28] which was supported by genetic evidence and feeding experiments using radioactive ^{34}S.[46] However, cysteic acid may be the preferred substrate, but cystine and Na_2SO_4 can also provide the sulfur

necessary for sulfonolipid production.[28,29] Furthermore, a mutant lacking the ability to produce cysteine was still able to produce sulfonolipids.[47] This shows, that much more research is needed to clarify the full biosynthetic pathway of sulfonolipid generation.

1.2 Chemical background

To better understand the molecular mode of action of both sphingo- and sulfonolipids in their biological context, isolation of the natural products alone is not sufficient. The occurrence of diastereomers in nature is challenging to analyze if the stereoisomers are difficult to separate with the standard analytical methods. Thus pure stereoisomers of each configuration are often needed for structure verification and can be supplied by total synthetic chemistry. By choosing an adequate route, the stereochemistry in the molecule is well defined, which allows for precise analytics. Comparison of the synthetic and natural samples then provides reliable insight into the 3D-structure of sphingo- and sulfonolipids. Furthermore, modifications (fluorescent tags for example) can be introduced with the help of synthetic chemistry, which allow to monitor the mode of action *in vivo* or alter the biological activity.[48] With this toolbox, a much deeper understanding of the biological operations can be achieved.

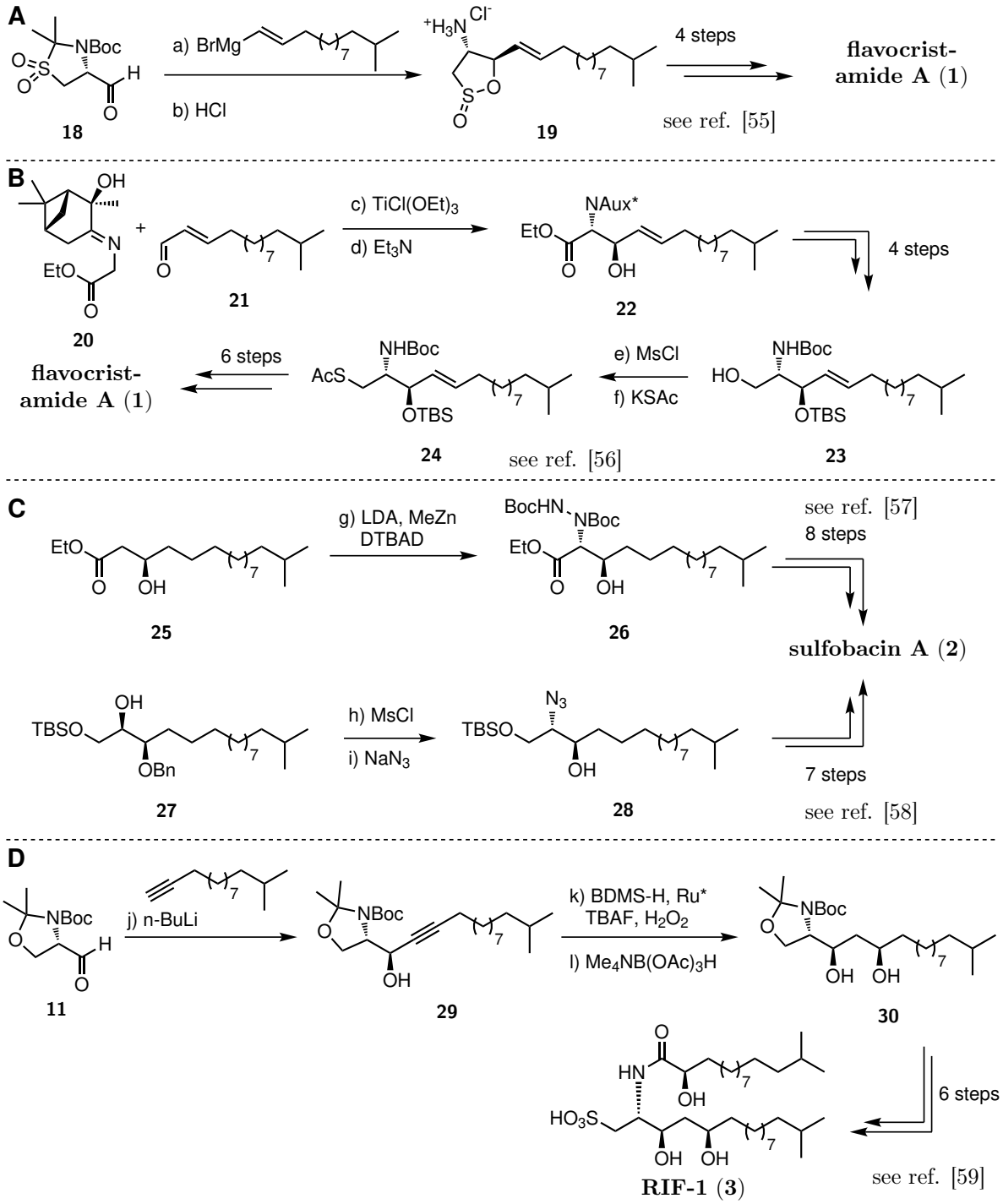
As such, many total syntheses of sphingolipids, and to a lesser extent also for 6-OH sphingolipids, have been described in the literature. Most of these start from the chiral pool (sugars, serine derivatives), whereas alkyne additions to Garner's aldehyde **11** are the favored routes.[49] Nucleophilic attacks are directed to the Re-face of the aldehyde according to the Felkin-Anh model due to the bulkiness of the Boc-group and fixation by the oxazolidine system resulting in an *anti*-configured product. In a separate step, the introduced triple bond is then reduced to the double bond, thus yielding the desired unsaturated ceramides.



Scheme 1.2: Key steps of reported 6-OH ceramide total syntheses.

This Garner-aldehyde strategy was also successful for the first total syntheses of the 6-OH sphingosine base and related ceramides reported in 2003 by the groups of Bittman, Yadav and Mori (scheme 1.2A).[50,53,54]

More recently, the employment of a cross-metathesis reaction enabled the construction of 6-OH sphingolipids as published by Overkleeft *et al.*; here a carbonate protecting group played an essential role for successful reaction outcome (scheme 1.2B).[51] Additionally, a sequence of *N*-oxidation, Meisenheimer rearrangement and aziridine ring opening reactions provided a completely different approach to 6-OH ceramides as published more recently by Yudin *et al.* (scheme 1.2C).[52]



Scheme 1.3: Key steps of reported sulfonolipid total syntheses.

Reports of sulfonolipid syntheses are more scarce in the literature and to date only the stereoselective total synthesis of the four sulfonolipids **1**, **2**, **3** and **5** have been described in the literature.

The synthesis of **1** by Takikawa *et al.* resembled in part the synthesis of sphingolipids by adding an alkyne to a sulfur analog of Garner's aldehyde **18** (scheme 1.3A).[55,60] The synthesis was completed by

peptide coupling and functional group manipulations, including oxidation of the sulfur to the sulfonic acid.

A different approach was pursued by Shiori *et al.*, where the alkyl chain was introduced by a titanium mediated asymmetric aldol addition with glycine derivatives (scheme 1.3B).[56,61,62] The carboxylic group at C-1 was reduced and the hydroxy group activated as mesylate followed by substitution with potassium thioacetate in a late stage S_N2-reaction. The sulfonic acid was available via deprotection of the thiol and oxidation in two steps, or directly by oxidation of the thioacetate with H_2O_2/TFA or oxone®/HOAc.

Another approach is the electrophilic amination pursued by Genêt *et al.* in their synthesis of **2** (scheme 1.3C).[57] Starting from a β-OH fatty acid, a Zn enolate was formed and trapped with an electrophilic amination reagent. The introduction of the sulfonic acid followed the method of Shiori *et al.* at a late stage.

The synthesis of sulfobacins has also been accomplished starting from glyceraldehyde derivatives by Chattopadhyay *et al* or α, β-dihydroxyacids in general by Kumar *et al.*[58,63]. Here, a nucleophilic substitution at C-2 was performed to introduce the nitrogen in the form of an azide. Instead of mesylation/substitution, the sulfonic acid was introduced here by Mitsunobu reaction of the alcohol at C-1 with thioacetic acid and subsequent oxidation, again at a late stage in the synthesis.

The synthesis of **3** and analogs was performed by adding an alkyne to Garner's aldehyde followed by a hydrosilylation/Tamao-Fleming oxidation sequence to introduce the second alcohol (scheme 1.3D). Similarly to Chattopadhyay *et al.*, the sulfonic acid was introduced late stage by Mitsunobu reaction and oxidation.

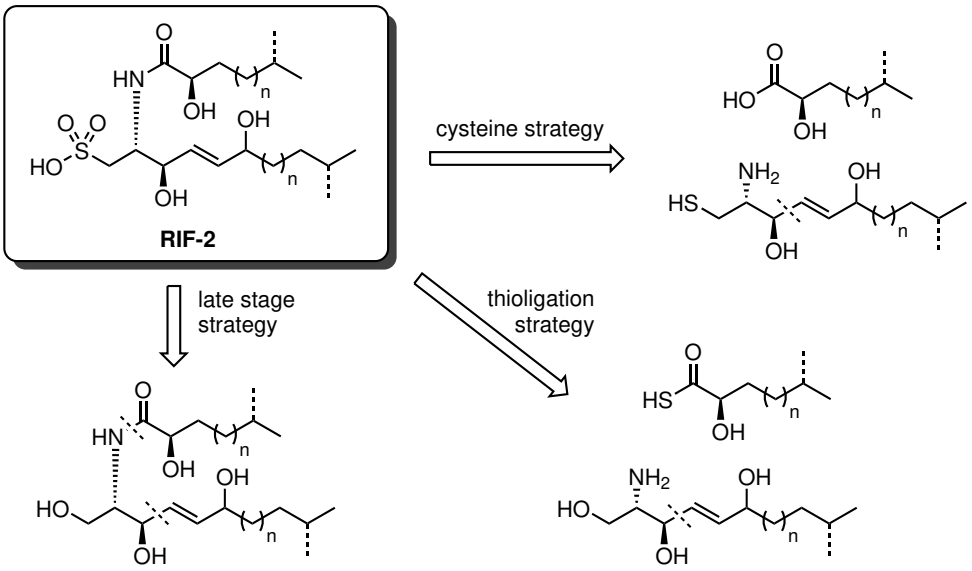
1.3 Aim and objectives of this thesis

Based on the findings, that **RIF-2** (**4**) induces multicellular colony formation, it provides an excellent target for a chemical total synthesis. Additional tools such as fluorescent labels or bio-orthogonal chemical handles are required to deepen the chemical understanding of the biological processes involved. The aim is thus, to create a short, stereo-defined, and modular synthesis of **RIF-2** (**4**) and analogs. In particular, the stereochemical implications of the C-6 OH group with the so far unknown stereochemistry should be thoroughly investigated.

In order to achieve this goal, the synthesis of ceramides following the Garner's aldehyde route should be investigated first to construct the building blocks required for sulfonolipid synthesis. Proceeding then to the synthesis of sulfonolipids, several strategies were designed based on previous literature reports (scheme 1.4). With the "cysteine strategy", cysteine would be used as starting point, followed by addition of alkyl chain and fatty acid later on, similar to the sulfonolipid synthesis by Takikawa *et al.*[55] This approach will be discussed first en route to sulfonolipids, followed by investigations towards the "thioligation strategy", which will rely on the formation of thioesters at C-1 followed by an intramolecular attack of the amine. This process would form the amide bond, leave the unprotected thiol at C-1 ready to be oxidized to the sulfonic acid and save steps by introducing fatty acid and sulfur simultaneously. This approach is inspired by the native chemical ligation, which is widely employed in the synthesis of larger peptides or the formation of macrocycles, but has not yet been used in the synthesis of sulfonolipids.[64,65]

The strategy investigated last is the "late stage strategy". Here, advantage is taken from the previously established synthesis of ceramides. A nucleophilic substitution at C-1 by a sulfur source should then form the sulfonolipids at the end of the synthesis. This is similar to the strategies already used for the total synthesis of sulfonolipids.

Once sulfonolipids have been assembled, they should be tested for their biological activity within the choanoflagellate model system.



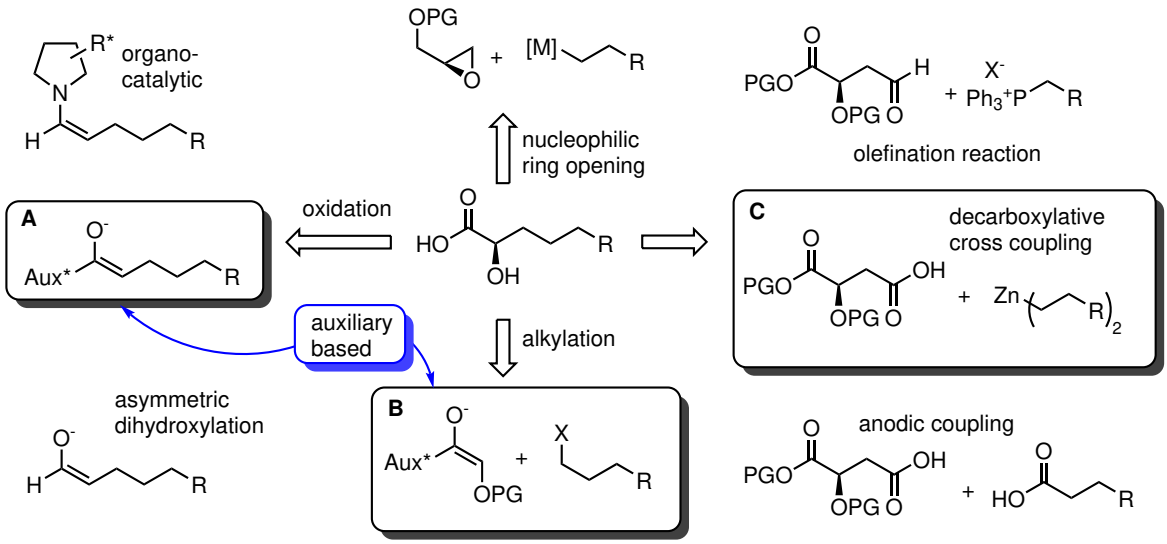
Scheme 1.4: Retrosynthetic approaches towards **4** and congeners.

2 The total synthesis of RIF-2 (4)

In the following chapters, the total synthesis of **RIF-2** (**4**) will be discussed according to the outlined synthetic strategies section 1.3. As such, the preparation of α-OH fatty acids will be discussed first, moving on to the synthesis of sphingosine and ceramides in the second part. The synthesis of sulfonolipids and comparison of analytical data with natural isolates will conclude this chapter.

2.1 Synthesis of α-OH fatty acids

Several synthetic approaches towards α-OH fatty acids have been described in the literature including the ring opening reaction of chiral epoxides,[66] enantio- or diastereoselective oxidation reactions of enolates or enamines,[67,68] the diastereoselective alkylation of auxiliary bound enolates[69–71] and the use of malic acid derivatives (scheme 2.1).[72,73]



Scheme 2.1: Overview of synthetic approaches towards α-OH fatty acids; A,B and C are discussed in the following sections.

The nucleophilic ring opening of chiral epoxides reaction provides an atom economic approach to chiral vicinal diols (scheme 2.1 top), which can then be transformed into the α-OH carboxylic acids by selective oxidation of the primary alcohol. The oxidation usually proceeds via the formation of an aldehyde. However, α-hydroxylated aldehydes are prone to epimerisation and hence this process needs to be performed with careful reaction control to not lose the stereo information.

α-Oxidation of aldehydes or enamines also faces the problem of loss of stereo information, however, this can be circumvented by the use of enamides (scheme 2.1 box A), which are less prone to epimerisation than aldehydes. As the carbon is already on the desired oxidation state, only mild deprotection conditions are necessary to transform the amide into the free carboxylic acid.

The disadvantage of oxidizing auxiliary bound fatty acids at a late stage lies in the early introduction of the alkyl chain, which requires further steps to access a wide substrate scope for larger product libraries.

Here, the diastereoselective alkylation of enols or enamides can be used (scheme 2.1 box B), which is characterized by the mild deprotection conditions of the oxidation route and offers the possibility of introducing a range of functional groups at a late stage of the synthesis by changing the alkyl electrophile.

Malic acid derivatives have scarcely been used in the literature to obtain α-OH-carboxylic acids (scheme 2.1 right), although the molecule provides both oxidation state and α-hydroxylation. One approach applies the Wittig-olefination of a malic acid aldehyde followed by hydrogenation to access longer chain fatty acids.[73] Despite its robustness, the high number of steps required and the low atom economy of the Wittig reaction render this approach impractical.

An alternative approach describes the undirected anodic coupling of a malic acid derivative with another carboxylic acid. Here cheap and abundant starting materials are used and the desired fatty acid is obtained in two steps, but only limited yields are reported for this process. The recently emerging decarboxylative cross-coupling reaction presents an interesting alternative. Originally developed as sp^2-sp^3-coupling between arenes and alkyl reagents,[74] the methodology was expanded later to the coupling two sp^3-centers via single electron transfer mechanisms.[75] Due to chemical modifications, this process is much more directed than the electrochemical one, but uses similar intermediates to the electrochemical coupling. Although without literature precedence, the idea came up to use malic acid derivatives in this radical process to access α-OH fatty acids (scheme 2.1 box C).

Considering step counts and efficiency of these approaches, three were selected for further investigation: Auxiliary based approaches A (oxidation) and B (alkylation) as starting points due to their abundance in literature and the new decarboxylative cross coupling approach C as interesting new conceptual approach to α-OH fatty acids.

2.1.1 Auxiliary-based approaches

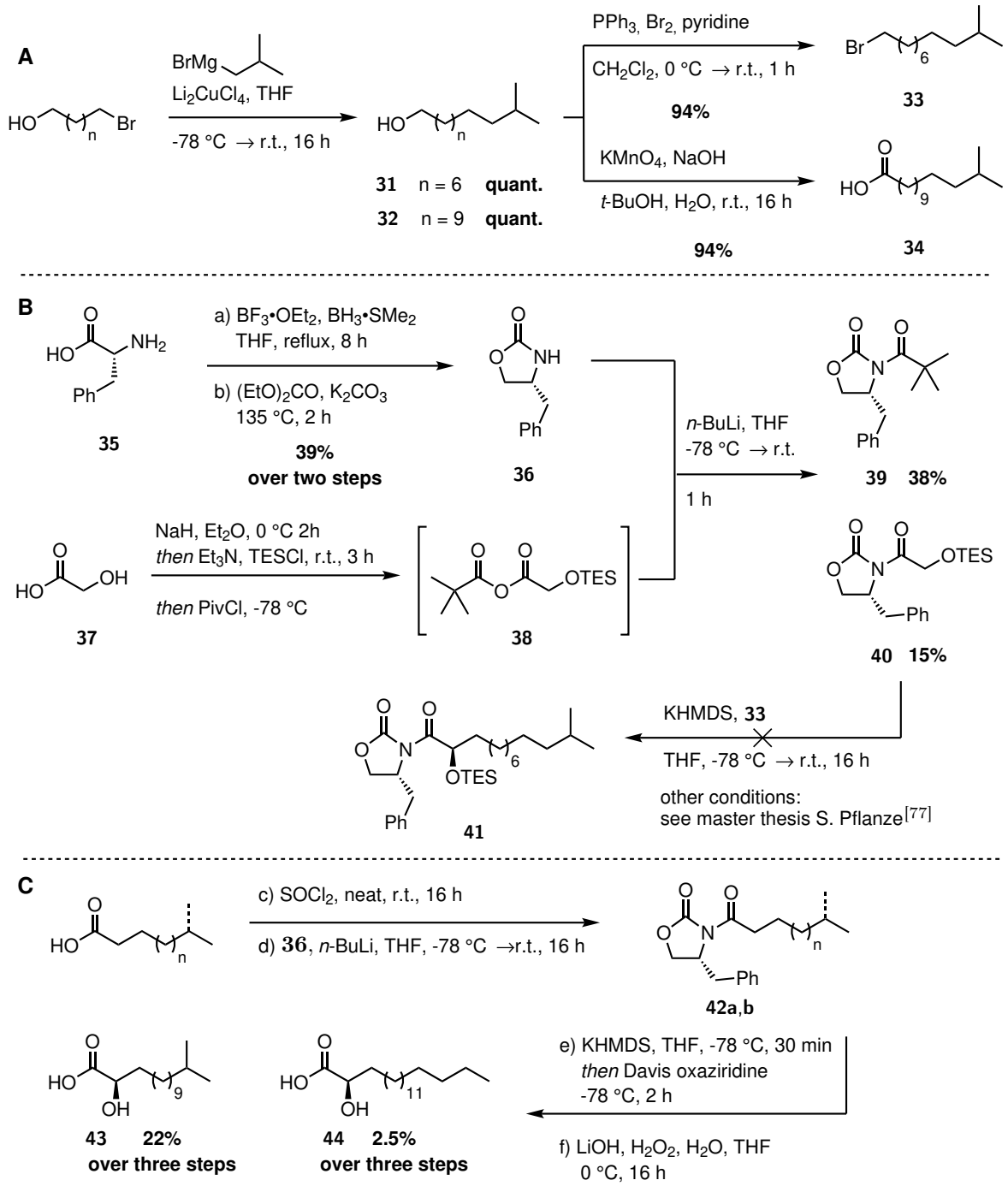
The two auxiliary based approaches shown in scheme 2.1 were selected for first studies. The alkylation pathway B was used as starting point, as it allows for a later derivatization in the fatty chain. To obtain a suitable electrophile for the alkylation reaction, bromide **33** was synthesized according to literature procedures (scheme 2.2A). First, the Cu-mediated coupling of *i*-butyl magnesium bromide and commercially available ω-bromo alcohol was performed followed by bromination with PPh_3, Br_2 and pyridine in 94 % yield over two steps.[76]

With a suitable electrophile in hand, the auxiliary was synthesized next by conversion of D-phenylalanine into the respective diol and subsequent ring closure yielding **36** in 39 % over two steps (scheme 2.2B), as reported in the literature.[78]

Then, the α-OH-carboxylic acid was introduced in the form of TES-protected glycolic acid, which was activated as a mixed anhydride and treated with deprotonated **36** in a one-pot fashion to give **39** as the major product (38 %) and the desired **40** as a minor product (15 %). The formation of **39** can be rationalized via an attack of the lithiated **36** on the carbonyl group belonging to pivaloic acid in the mixed anhydride **38**. This attack should be kinetically disfavored due to the steric hindrance of the *tert*-Butyl group and low reaction temperatures should diminish the formation of this by-product. Indeed, optimization of the reaction parameters by Pflanze increased the yield of **40** to 42 %.[77]

With both fragments in hand, their combination towards α-OH fatty acids was investigated. Despite variations in solvent, base and temperature, no conversion to the desired elongated product was observed (see also reference [77]). Therefore, the alternative approach using diastereoselective oxidation of an auxiliary bound fatty acid was investigated (scheme 2.1 box A).

The required carboxylic acid **34** was obtained *via* the $KMnO_4$/NaOH-based oxidation of branched alcohol

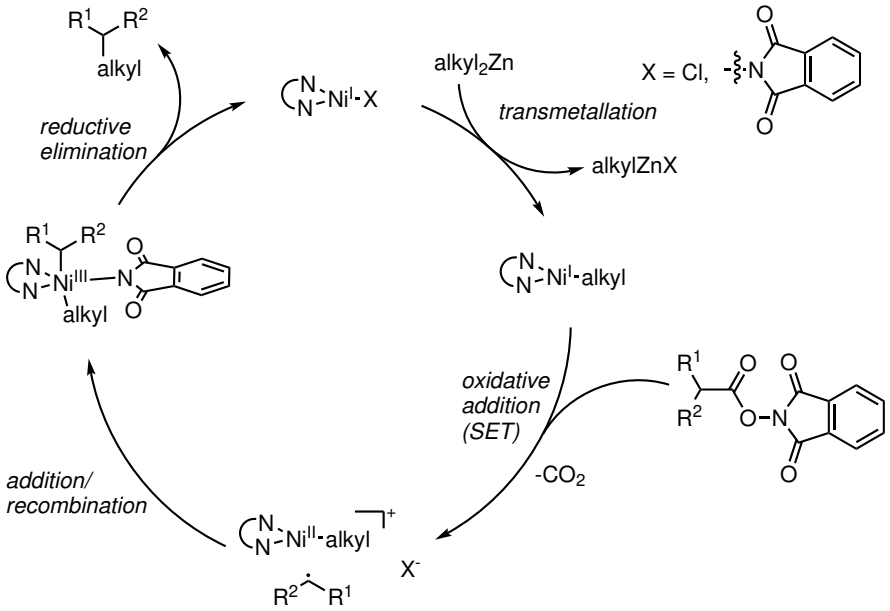


Scheme 2.2: Synthesis of α-OH-fatty acids using Evans' auxiliary **36**.

32 in 94 % yield (scheme 2.2A) or, in case of the linear stearic acid, commercially available material. Subsequent conversion to the acid chloride and coupling with deprotonated Evans' auxiliary **36** furnished auxiliary bound acyl compounds **42a** and **42b** (scheme 2.2C). The enolate formation was performed with KHMDS and the addition of Davis oxaziridine **SI-3** at −78 °C yielded α-hydroxylated compounds **45** and **46**.[79,80] To finalize the synthesis of α-OH carboxylic acids, the auxiliary was cleaved using mild saponification conditions with H_2O_2/LiOH.[81] However, the low yields of 22 % for **43** and 2.5 % for **44** (scheme 2.2C) severely hindered larger scale reactions. High steric hindrance and difficulties during the purification of the carboxylic acid are the main reasons for these low yields even under optimized reaction procedures.

2.1.2 Decarboxylative cross-coupling approach

In an alternative approach, the decarboxylative cross-coupling was investigated next. In 2016, the Baran group reported a general approach to the radical cross coupling of carboxylic acids with Zn-organyls, showcasing the generality of the reaction with a a wide range of aromatic and aliphatic carboxylic acids combined with various Zn-organyls.[75] The mechanism of action involves the transmetallation from the Zn-organyl to the Ni-catalyst as initiating step (scheme 2.3). In a single-electron transfer (SET) process, the activated carboxylic acid is decarboxylated and the resulting alkyl radical transferred to the catalyst. A reductive elimination step releases the coupled product and restores the Ni-catalyst.

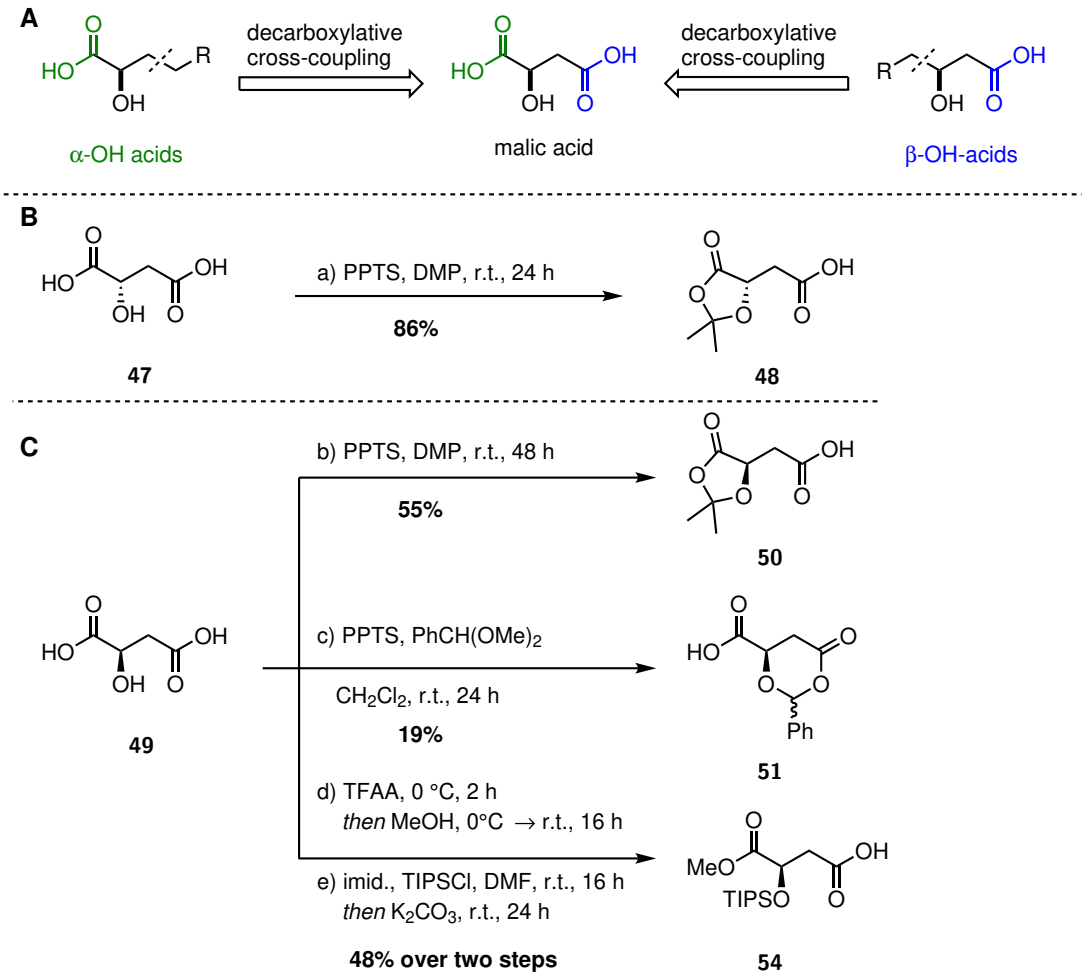


Scheme 2.3: Proposed mechanism of the decarboxylative cross-coupling.[75]

Applying this methodology to the synthesis of α-OH fatty acids requires a chiral α-OH diacid as starting material, as found in malic acid. In 1954, an article was published, which utilized malic acid in an anodic coupling reaction to generate α-OH fatty acids electrochemically.[72] The success in this rather undirected radical process implies, that malic acid may be used in the decarboxylative cross coupling reaction, although it has not been reported yet. Intriguingly, different protecting group strategies allow the selective decarboxylation of one of the two acids, giving access to α-or β-OH fatty acids (scheme 2.4A). Although there is no precedent in the literature, this new method is among the most step economic approaches to hydroxylated fatty acids.

To test the hypothesis that malic acid can be used in the decarboxylative cross coupling reaction, four protected malic acid derivatives were synthesized as putative starting materials in a step efficient manner. The most step efficient approach is the synthesis of literature known acetonides **48** and **50**, which were obtained by the reaction of L- or D- malic acid with catalytic amounts of PPTS in DMP at r.t. in 55 – 86 % yield (scheme 2.4).[82] Similarly benzylidene acetal **51** was obtained by the reaction of D-malic acid with benzaldehyde dimethyl acetal and catalytic amounts of PPTS in CH_2Cl_2 in 19 % yield. Despite several optimization attempts, only small improvements in yield were achieved, probably due to the high lability of the acetal towards the inherent acidity.[83]

Due to the use of a joint protecting group for the OH and carboxy groups, all three derivatives provided a fully deprotected α-OH fatty acid when only one of the two groups is deprotected. For some applications, however, a protecting group is necessary, so the orthogonal protecting groups methyl ester and silyl ether were incorporated into **54** in two steps from D-malic acid.



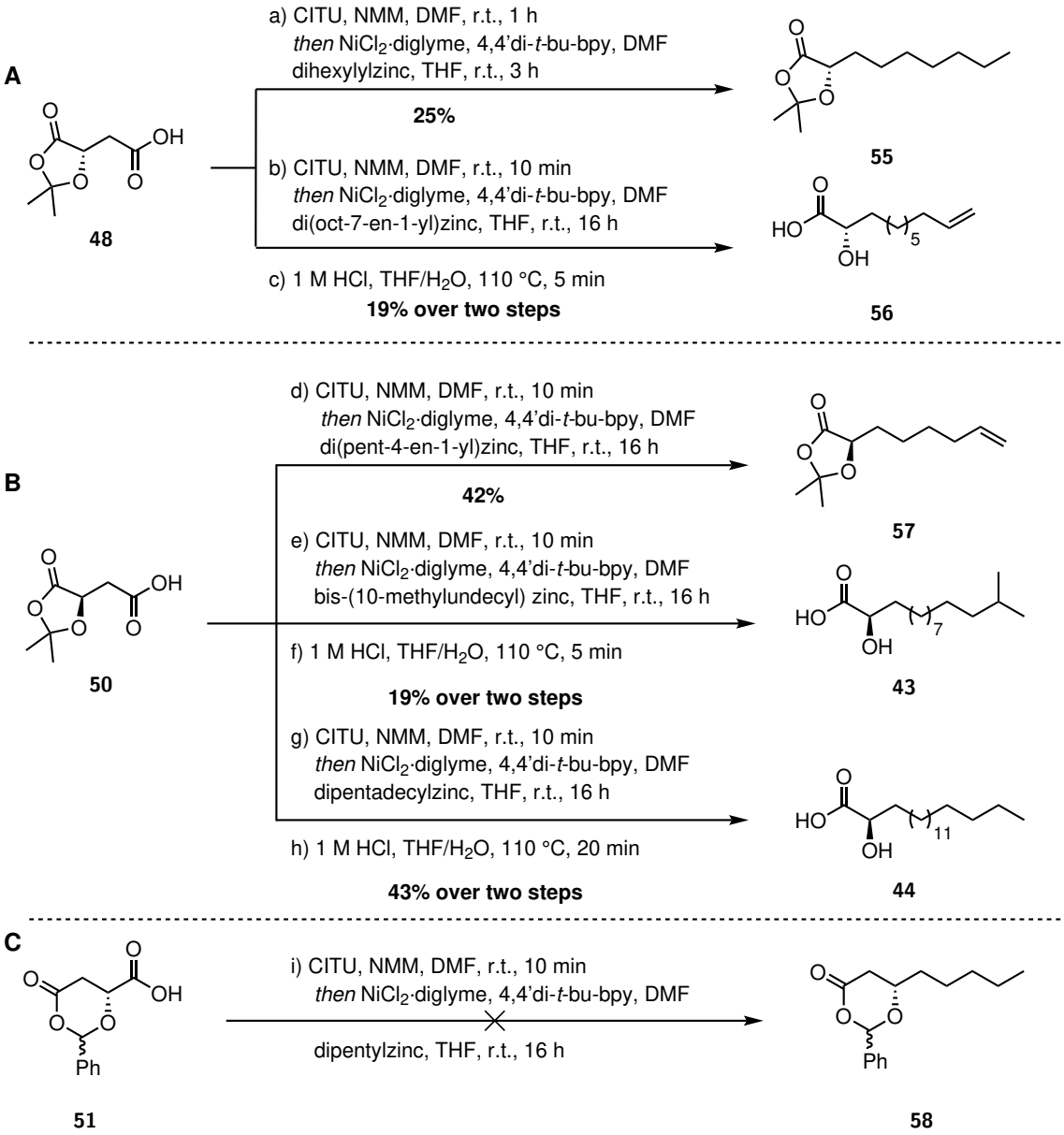
Scheme 2.4: A) Retrosynthetic considerations for the synthesis of hydroxylated fatty acids starting from malic acid; B) synthesis of L-malic acid derivative **48**; C) synthesis of D-malic acid derivatives **50**, **51** and **54**.

To achieve the selective esterification, two synthetic ways are possible. The first is the reaction of D-malic acid with TFAA, in which a mixed anhydride is formed, which then reacts with methanol to yield the methyl ester **52** in 56 % yield (scheme 2.4).[84] As a side product, dimethyl ester **53** was isolated in 36 % yield.

The second approach was described by HOUSTON *et al.* and utilizes the coordination of boric acid to the hydroxy group, which results in the preferential formation of the five membered heterocyclic mixed anhydride over the six membered ring analog.[85] The activated carboxy group reacts with methanol to yield the ester **52** in 47 % albeit with decreased purity compared to the product obtained in the reaction with TFAA. Thus, the TFAA methodology is the preferred approach to methyl ester **52**.

Moving on to the OH-protecting group, silylation of both carboxy and hydroxy group was achieved with two equivalents of TIPSCl and imidazole. The silyl ester was subsequently saponified with K_2CO_3 to the carboxylic acid **54** in 86 % yield.[86]

The obtained malic acid derivatives were then subjected to decarboxylative cross coupling reaction conditions. As a first test reaction, acetonide-protected **48** was coupled with dihexylzinc using *in situ*activation with CITU (scheme 2.5A).[87] After the purification, the product was isolated in 25 % yield. The coupling with di(oct-7-en-1-yl)zinc and subsequent deprotection with 1 M HCl in THF/H_2O furnished carboxylic acid **56** in 19 % yield over two steps.



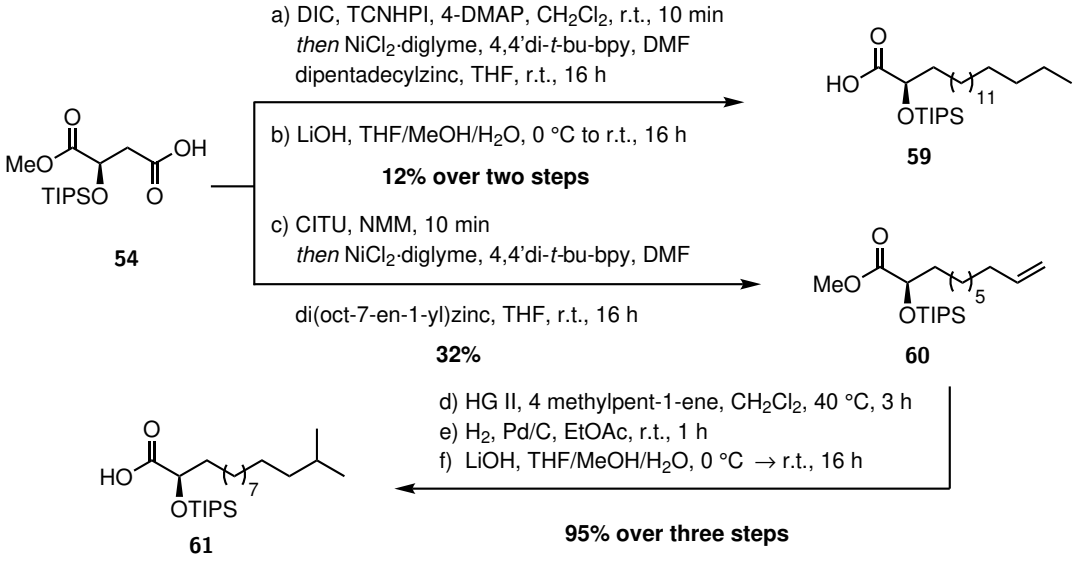
Scheme 2.5: Decarboxylative cross coupling reactions with ketal derived carboxylic acids to A) (*2S*)-OH fatty acids; B) (*2R*)-OH fatty acids; C) (*3S*)-OH fatty acids.

Following the optimization of the reaction conditions (reaction times, activation procedure), carboxylic acid **50** was coupled with di(pent-4-en-1-yl)zinc in 42 % yield (scheme 2.5B). The use of bis-(10-methylundecyl)zinc and dipentadecylzinc as coupling partners then furnished acetonides **SI-7** and **SI-9**, which were both deprotected to yield the fatty acids **43** in 19 % and **44** in 43 % over two steps, respectively. The deprotection was performed under microwave conditions (110 °C for 5 min) in contrast to previous literature reports (60 °C for 48 h).[73]

The major obstacle in the coupling/deprotection sequence appeared to be the Grignard reagent formation, as concurring Wurtz reactions on the longer chain derivatives reduced the amount of organometallic compound available. In general, higher yields were obtained when commercially available Grignard solutions were used for the generation of organozinc species (e.g. for **SI-7**). Furthermore, it was found that the branching in alkyl chain influences the reaction outcome as well. The Grignard reagents for the synthesis of linear fatty acid **56** and branched fatty acid **44** were both self-prepared, yet the yields differ significantly.

With only three synthetic steps, this method provides rapid access to α-OH fatty acids. The application of this strategy for the generation of β-OH-fatty acids from benzylidene acetal **51** and dipentylzinc was tested by M. Zimmer in the context of his internship.[88] Although the organo zinc reagents were prepared from commercially available pentyl magnesium bromide, no product **58** was observed (scheme 2.5C). Most likely, the lability of the benzylidene moiety towards reductive conditions is the cause of decomposition of the starting material, as no product was isolated in these reactions.[89] It can be further speculated that other acetals (e.g. pivaloyl acetal) or the use of a different protecting group strategy would be more suitable for the production of β-OH fatty acids in higher yields.

To follow up on the orthogonal protecting group strategy for the synthesis of α-OH fatty acids, the coupling of TIPS-protected methyl ester **54** with dipentadecylzinc and di(oct-7-en-1-yl)zinc was investigated. To check whether increased yields are obtained when the isolated redox active ester is used,[75] the first reaction of **54** was performed with DIC and TCNHPI as activating agents and the active ester was then coupled with dipentadecylzinc. Saponification of the methyl ester using a mixture of THF and MeOH with aqueous LiOH then furnished TIPS-protected carboxylic acid **59** in 12 % over two steps. The solvent mixture was considered crucial, as the use of either solvent alone only resulted in an emulsion and lower yields compared to the solvent mixture. No significant increase in yield was observed upon isolating the redox active ester, thus the *in situ* activation using CITU was used again for the coupling with di(oct-7-en-1-yl)zinc to obtain methyl ester **60** in 32 % yield. The alkene moiety was then extended using cross metathesis, hydrogenation and saponification to yield TIPS-protected fatty acid **61** in 95 % yield over three steps.



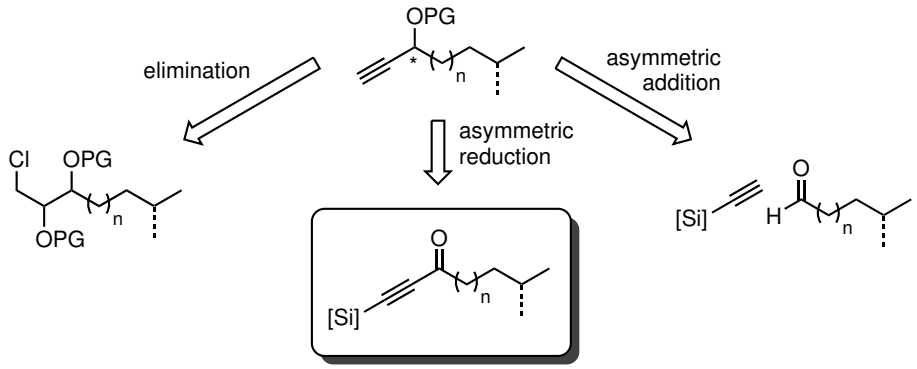
Scheme 2.6: Synthesis of silyl protected α-OH carboxylic acids.

In total, the decarboxylative cross-coupling strategy furnished three fully deprotected α-OH-fatty acids, two acetonide protected fatty acids and two silyl protected fatty acids in varying yields (12 – 43 %), but in only three to six steps starting from malic acid. The outlined synthetic route proofed suitable to generate **61** and also to introduce functional tags or reactive warheads in the fatty chain *via* cross metathesis. Its application in biological studies was shown by Raguž *et al.*[90]

2.2 Synthesis of unnatural ceramides

2.2.1 Synthesis of the alkyne building blocks

After establishing a new route to chiral α-OH-carboxylic acids, a selective access to both C-6 stereoisomers of the sphingoid core structure was sought next. To achieve this goal, the stereocenter can be introduced by either a protected alcohol at the beginning or in the form of a protected ketone later in the synthesis. An adjacent alkyne functionality constitutes a masked double bond between C-4 and C-5, making propargylic alcohols or ketones suitable intermediates. As depicted in scheme 2.7, several enantio- or diastereoselective approaches to propargylic alcohols have been described in the literature.



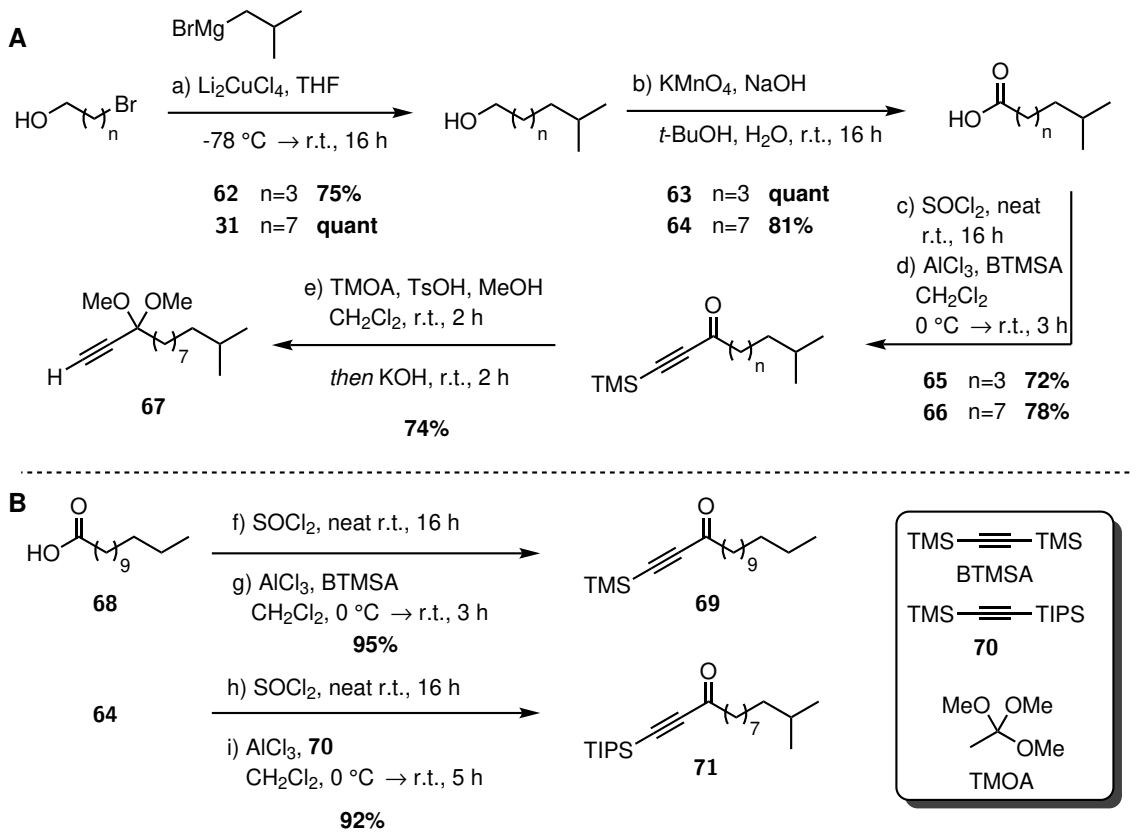
Scheme 2.7: Overview of synthetic approaches towards chiral propargylic alcohols.

The double elimination of halohydrins as described by Bittman *et al.* using a lengthy reaction sequence leads to chiral propargylic alcohols in excellent enantioselectivities.[91] In this case, the stereochemistry was established with an asymmetric dihydroxylation, but the required six synthetic steps from commercially available starting materials make this approach less suitable for larger scale. Another possibility is the enantioselective addition of acetylene derivatives to aldehydes.[92] However, this direct route suffers from the instability of aldehydes and the need to establish a good enantioselective addition reaction, which usually requires exhaustive ligand screening.

The enantioselective reduction of acetylenic ketones offers a third possibility.[93] This asymmetric hydrogen transfer reaction can be mediated by chiral Ru complexes[94,95] or by proline-derived boranes,[93,96,97] to name only the most prominent examples. This approach describes a sequence, that is only one synthetic step longer than the addition reaction.

From these three approaches the asymmetric transfer hydrogenation was chosen for first investigations. Therefore the synthesis of acetylenic ketones was examined (scheme 2.8), which can be prepared by a Friedel-Crafts-like reaction of carboxylic acid chlorides with bis-silyl alkynes mediated by $AlCl_3$.[98] The yields for this process range from 72 to 95 % on multi-gram scale. To obtain a building block for a late stage ketone introduction, **66** was converted into the dimethyl ketal followed by *in situ* TMS-deprotection using KOH in 74 % yield. During reduction reactions, a more stable protecting group on the alkyne may prove useful;[97,99] hence, the more stable TIPS-group was introduced by using unsymmetrical acetylene derivative **70** in 92 % yield (scheme 2.8B).[97] The stronger electron donating effect of the TIPS group in comparison to the TMS group leads to an increased electron density at its β-position, making that carbon more nucleophilic and more likely to attack the activated acyl chloride.[100]

Proceeding in the synthesis, alkynones **66** and **69** were reacted with non-chiral reducing agent $NaBH_4$ to obtain a racemic standard for later *ee*-determination. As a result, not only the expected alkynols **72** and **74** were obtained, but also TMS-deprotected **73** and **75** (scheme 2.9A). This result is intriguing, since $NaBH_4$-induced TMS-cleavage from alkynes has not yet been reported. It can be speculated that



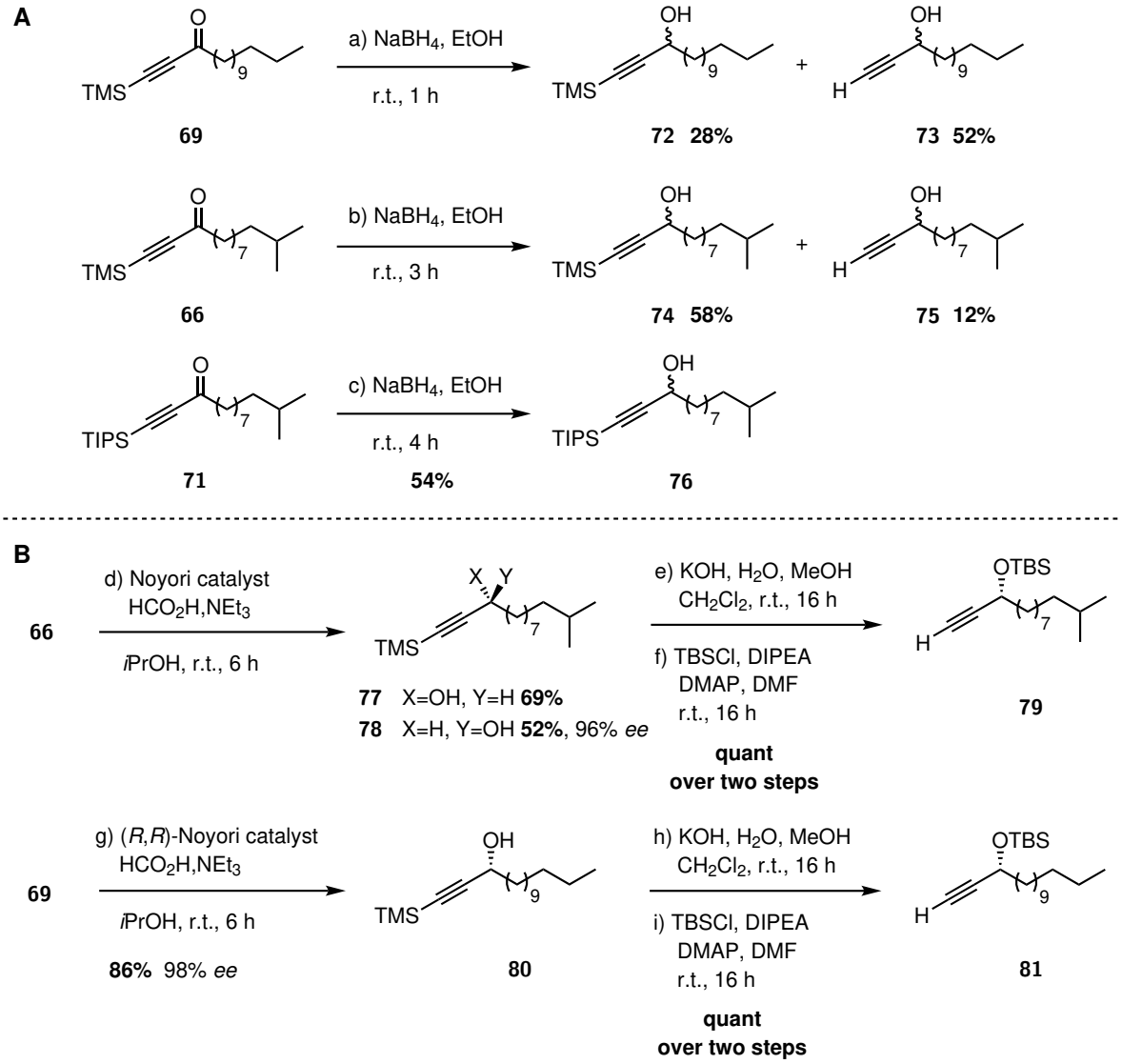
Scheme 2.8: A) Synthesis of ketal **67**; B) synthesis of propargylic ketones **69** and **71**.

boron alkoxylates, which form after successful reduction, work as Lewis bases and cause the C-Si-bond to break. For example, TMS-cleavage was observed for electron poor alkynone systems with inorganic borate salts, supporting this hypothesis.[98] However, attempted TMS deprotection of propargylic alcohol **74** with $Na_2B_4O_7$ resulted only in the recovery of the starting material. This may indicate, that the alkynone **66** is likely deprotected by newly formed boron alkoxylates prior to reduction.

Another appealing possibility is the deprotection via the base induced Brook rearrangement, in which the silyl group migrates from a carbon to an alcohol in the present case to form a TMS-ether.[101] This rather labile protecting group is either cleaved during the reaction or the acidic work-up. Interestingly, larger silyl groups migrate at a similar rate as the TMS-group in a Brook rearrangement, but the resulting larger silyl ether should be more stable to cleavage conditions. To verify this hypothesis, TIPS-protected alkynone **71** was submitted to reduction conditions with $NaBH_4$, which resulted only in C-silylated alkynol **76** in 54 % yield and without any O-silylated product (scheme 2.9 reaction c). This result clearly rules out a Brook rearrangement and further supports the Lewis base hypothesis.

With a racemic standard of alcohols **72**, **73**, **74** and **75** at hand, the enantioselective synthesis thereof was investigated next. Alcohols **77**, **78** and **80** were synthesized in a first attempt *via* Noyori's Ru-catalyzed asymmetric transfer hydrogenation with *i*PrOH and formic acid as hydrogen sources in 52 – 92 % yield.[99,102,103] The enantiomeric excess was determined by the esterification with 4-bromo benzoyl chloride followed by chiral HPLC analysis (96 – 98 % compared to the racemic standard).

To finalize the synthesis of enantiomerically pure alkynol building blocks, C-deprotection was required, which was achieved with KOH and a CH_2Cl_2/H_2O/MeOH-mixture using phase-transfer conditions. Finally, standard silyl protection using TBSCl in DMF furnished silyl ethers **79** and **81** in quantitative yield over two steps.



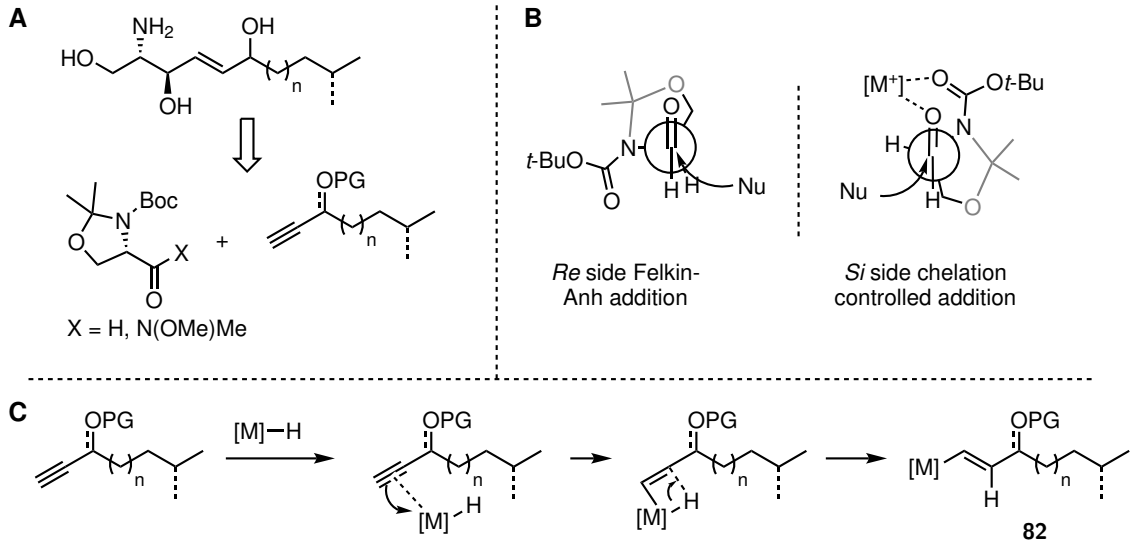
Scheme 2.9: A) Racemic synthesis of propargylic alcohols; B) enantioselective synthesis of protected propargylic alcohols.

2.2.2 Hydrometallation approach for the synthesis of (*3S*)-isomers

After successful construction of the alkyne building blocks with the defined stereochemistry at C-6, the introduction of the C-3 stereocenter was investigated next. The usage of Garner's aldehyde is well known for its diastereoselective addition reactions following the Felkin-Anh model in which one face of the carbonyl group is shielded by the bulky N-Boc-substituent in α-position.[104] The five-membered oxazolidine ring further fixes this conformation, resulting in improved diastereoselectivies for the Re-face addition of nucleophiles (scheme 2.10B).[105] Interestingly, diastereoselectivity can be reversed under chelating conditions as some metal cations complexate the carbonyl oxygens of the Boc-group and aldehyde, resulting in a Si-face attack of nucleophiles (scheme 2.10B).

Intriguingly this chelate control can be performed with Zn-organyls, which themselves are available by the transmetallation from other organometallic reagents.[105] In hydrometallation reactions, a metal hydride is added *cis* to a triple bond and ends up at the least hindered, terminal position *trans* to the alkyl chain (scheme 2.10C). As a result, the allylic alcohol is constructed during a single reaction.

The idea was to manipulate the reaction conditions so that both (*3R*) and (*3S*) configurations could be constructed in a controlled manner from the same starting molecule, beginning with the less explored



Scheme 2.10: A) Synthetic approach towards sphingoid bases; B) different reactive conformations of Garner's aldehyde **11**; C) mechanism of the hydrometallation reaction.[106]

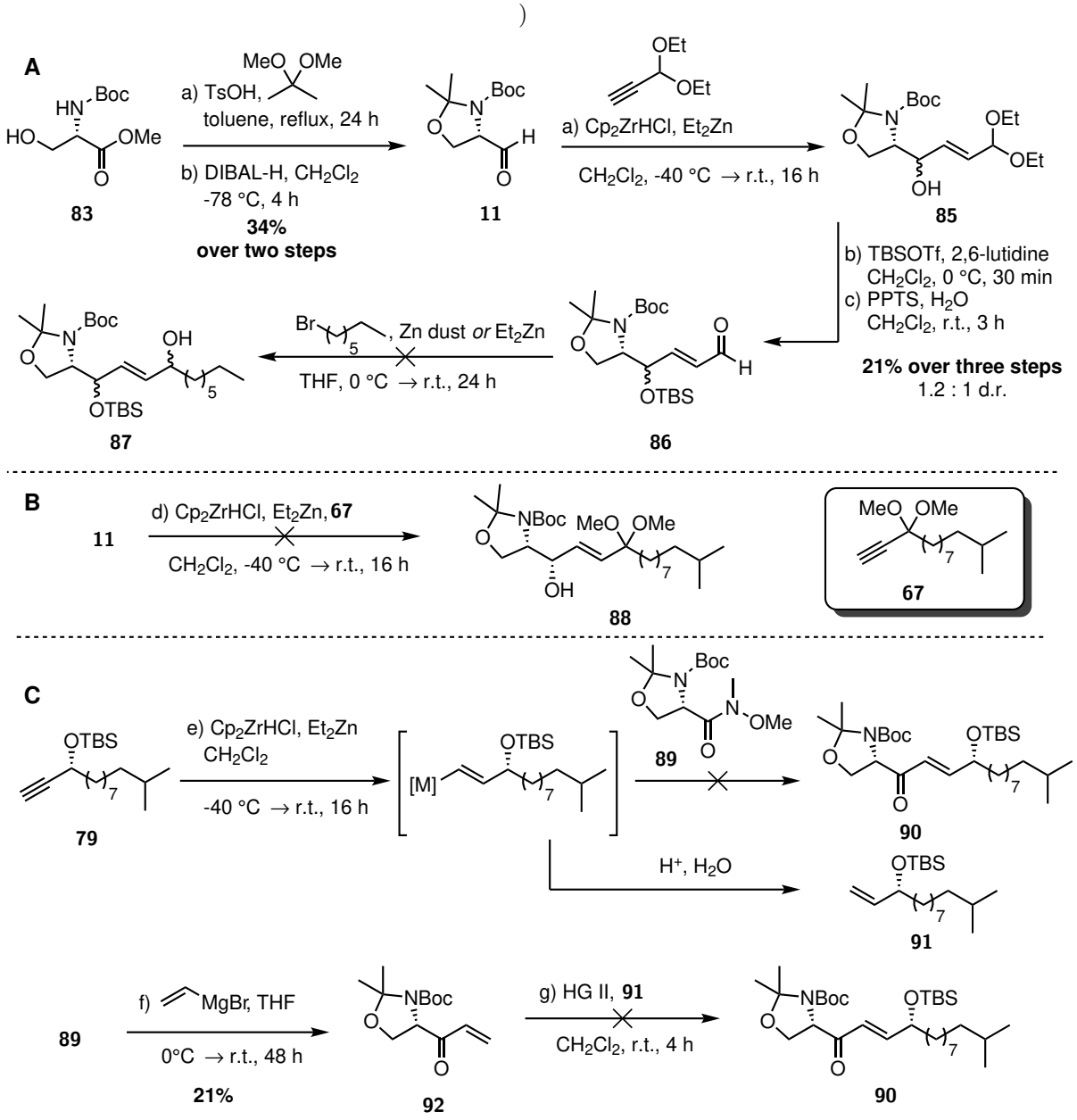
(*3S*) isomer.

Thus, Garner's aldehyde **11** was synthesized in 34 % over two steps from commercially available serine derivative **83** in multi-gram scale following the literature procedure (scheme 2.11A).[107] To test the hydrometallation/transmetallation approach with model substrates, 3,3-diethoxy-1-propyne was chosen as commercially available alkyne. Then, Cp_2ZrHCl (also named Schwartz' reagent) was used to reduce commercially available 3,3-diethoxy-1-propyne, followed by transmetallation of the Zr-complex to the organozinc species using Et_2Zn and addition to Garner's aldehyde **11** (scheme 2.11A). Due to suspected instability, the free OH-group was silyl protected using TBSOTf, during which partial acetal cleavage was observed. Hence, the acetal was then completely removed using PPTS in acetone, which furnished allylic aldehyde **86** as a 1.2:1 diastereomeric ratio in 21 % yield over three steps. This exemplified, that the general approach using Schwartz' reagent worked, however improved reaction conditions were required for higher yields and diastereoselectivies in the addition reaction.

Taking advantage of the carbonyl group at C-6, the stereoselective addition with Zn reagents to aldehydes was investigated using a chiral ligand developed by Knochel *et al.*.[108] However, no product formation was observed under the tested conditions (bromo hexane combined with Zn dust or Et_2Zn).[109] This may be due to an incomplete formation of organozinc species, although Et_2Zn should have added to the aldehyde as well, even if no other organozinc species was formed. Although a solution to this problem may be the use of Grignard reagents followed by transmetallation with $ZnCl_2$ as shown earlier (scheme 2.5 and scheme 2.6), different approaches seemed more promising.

As such, the hydrozirconation reaction was then performed with ketal **67** carrying the carbonyl group at C-6, which would allow for a late stage stereoselective reduction. However, the reaction failed to give any product (scheme 2.11B). It is plausible, that the ketal group is cleaved by the Lewis acidic Zn-reagents in the reaction mixture and then undergoes decomposition reactions.[110]

To circumvent these setbacks, the use of alkynol **79** in the hydrozirconation reaction was investigated next, as it already contains a more stable protecting group at C-6. This comes at the cost of an early stage introduction of the C-6 stereochemistry. To still introduce late stage variety, Weinreb amide **89** (available in a single step from oxazolidine methyl ester **84**) was chosen as electrophile. The advantage of such a functionality lies in the reactivity towards organometallic reagents: with stabilization of the tetrahedral intermediate that occurs after the nucleophilic addition of metal organyls to the carbonyl



Scheme 2.11: A) Synthesis of **87** using the hydrometallation approach; B) hydrozirconation of **67**; C) synthesis of **90** via hydrozirconation or cross-metathesis reactions.

group, the Weinreb amide is able to provide ketones instead of alcohols. However, the only product isolated in the reaction using Schwartz' reagent, Et_2Zn and Weinreb amide **89** was allylic TBS ether **91** (scheme 2.11C), indicating a successful hydrozirconation reaction followed by hydrolytic cleavage. It can be speculated that the decreased electrophilicity of the Weinreb amide compared to the aldehyde prevents addition reactions by Zn organyls.

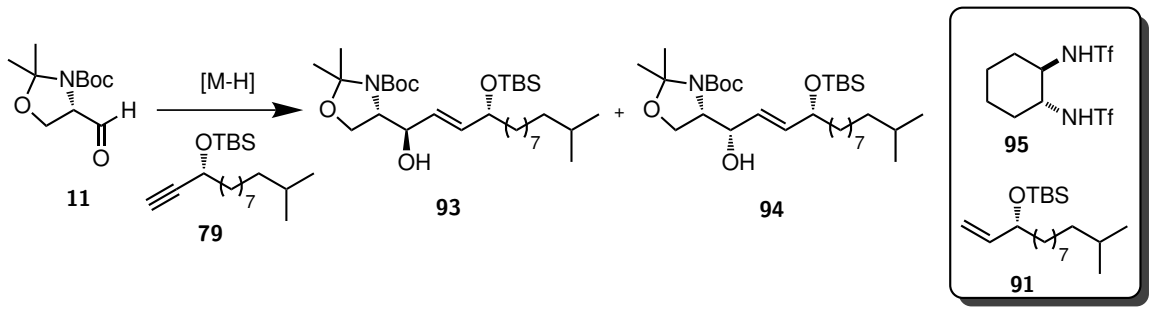
To avoid this problem, the cross metathesis between allylic ketone **92** and allylic TBS-ether **91** was investigated. Therefore **92** was synthesized in 21 % yield from the Weinreb amide **89** and vinyl magnesium bromide, and then subjected to cross metathesis reaction conditions with **91**. However, the desired product **90** was not obtained under the tested conditions and only 14 % of the ketone were re-isolated.

This indicates, that introduction of a carbonyl group at C-3 requires a specific set of reaction conditions or a multi step procedure. For example, instead of transmetallating the Zr-complex **82** with Et_2Zn, it may be quenched with I_2 to yield the vinyl iodide, which then can undergo lithium halide exchange or

Grignard reagent formation, thereby serving as nucleophile.[111,112] Another approach to the carbonyl group at C-3 not involving the Weinreb amide is the Liebeskind-Srogl reaction between a thioester and a boronic acid with catalytic Pd and stoichiometric Cu.[113,114] However, to apply these conditions, the synthetic route needs to be adapted to provide the different educts. Lastly, the oxidation of an alcohol at C-3 also leads to the formation of the carbonyl group. Though not very step-efficient, this approach can be easily applied to the synthesis of sphingolipids, as they contain an alcohol at C-3 anyway.

Thus, further investigations were performed to evaluate the introduction of the C-3 alcohol using different hydrometallation reagents (e.g. Dibal-H, Red-Al® etc.) together with protected alkynols **79** and **81**. As shown in table 2.1, only Schwartz' reagent afforded a reasonable transformation of **79** among the tested reagents, which lead to the isolation of alkene **91** in up to 86 % yield. However, no addition product to Garner's aldehyde **11** was obtained. Supplementation of the hydrozirconation reaction mixture with Et_2Zn achieved the addition to the aldehyde, yielding a diastereomeric mixture of **91** and **94** with a slight preference for the *anti*-product in 33 % yield. The reaction time, temperature and various additives were tested in order to increase yields and the selectivity of the addition reaction. The most pronounced increase in yield was observed when the reaction mixture was slowly warmed to r.t. over a longer period of time after transmetallation (entry 8). These conditions also resulted in the slightly preferred formation of chelate-controlled *syn*-product **94**. It can be speculated whether the chelation of carbamate and aldehyde occurs through the newly released Cp_2Zr species or the Zn organyl itself Even higher yields were obtained when the reaction was performed on a bigger scale (entry 11). Lower yields were observed upon the addition of stronger Lewis acids ($ZnBr_2$, $BF_3{\cdot}OEt_2$),[51,115] presumably due to deprotection or isomerization reactions.

Table 2.1: Optimization of the hydrozirconation reaction



[M−H]	additive	temperature	time	solvent	yield	**93** : **94**
DIBAL-H[a]	—	r.t. → 60 °C	1 h	toluene	—	—
Red−Al[a]	—	−15 °C → r.t., then 60 °C	72 h	THF	—	—
catechol-borane[a]	Et_2Zn	r.t., then 60 °C	48 h	CH_2Cl_2	—	—
dicyclohexyl-borane[a]	Et_2Zn	0 °C → r.t., then 60 °C	48 h, then 1 h	CH_2Cl_2	—	—
Cp_2ZrHCl[a]	—	0 °C → r.t.	3 h	CH_2Cl_2	—	—
Cp_2ZrHCl[b]	Et_2Zn	−40 °C → r.t.	4 h	CH_2Cl_2	33 %	1.3 : 1.0
Cp_2ZrHCl[b,d]	Et_2Zn	−40 °C → r.t.	16 h	CH_2Cl_2	29 %	1.3 : 1.0
Cp_2ZrHCl[b,e]	Et_2Zn	−40 °C → r.t.	16 h	CH_2Cl_2	50 %	1.0 : 1.4

[M−H]	additive	temperature	time	solvent	yield	**93** : **94**
Cp_2ZrHCl[b,c,e]	Et_2Zn	−40 °C → r.t.	16 h	CH_2Cl_2	61 %	1.0 : 3.3
Cp_2ZrHCl[b]	Et_2Zn, $BF_3{\cdot}OEt_2$	−78 °C → 0 °C	6 h	CH_2Cl_2	12 %	1.0 : 1.7
Cp_2ZrHCl[b]	Et_2Zn	−40 °C → r.t.	3 h	THF	15 %	2.7 : 1.0
Cp_2ZrHCl[b,c]	$ZnBr_2$	0 °C → r.t.	16 h	THF	18 %	n.d.
Cp_2ZrHCl[b]	Et_2Zn	−40 °C → r.t.	4 h	toluene	24 %	2.4 : 1.0
Cp_2ZrHCl[b]	Et_2Zn, $Ti(OiPr)_4$, 8 mol % (*R*,*R*)-**95**	−78 °C → −20 °C	16 h	toluene	39 %	1.0 : 1.3
Cp_2ZrHCl[b]	Et_2Zn, $Ti(OiPr)_4$, 8 mol % (*S*,*S*)-**95**	−78 °C → −20 °C	16 h	toluene	65 %	1.0 : 2.4

[a] Reaction was performed according to GP 16; [b] reaction was performed according to GP 17; [c] alkynol **81** was used; [d] the cooling bath was removed after 1 h; [e] the reaction was slowly warmed to r.t. over night.

Moderate yields with a slight preference for the *anti*-product **91** were observed when toluene was used as solvent. However, a change in selectivity towards the *syn*-isomer was observed after the addition of the chelating Lewis acid $Ti(OiPr)_4$ and chiral ligand (*R*,*R*)-**95**.[116] Interestingly, the preferred formation of *syn*-isomer **94** was caused by the enantiomeric ligand (*S*,*S*)-**95** as well, also accompanied by a further increase in the total yield from 39 to 63 %, indicating a better matching ligand-substrate pair.

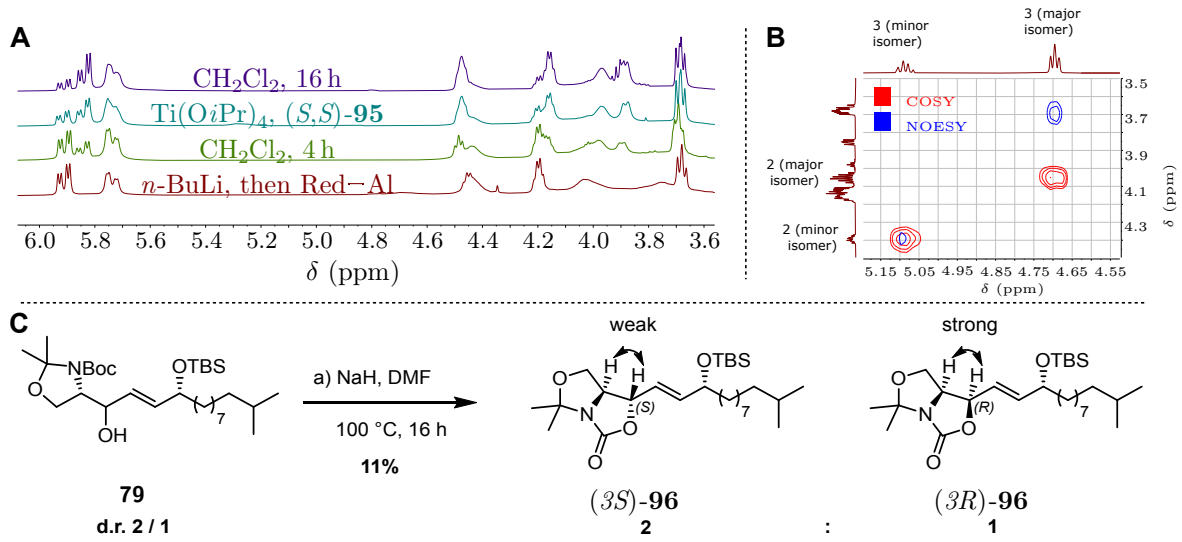
As depicted in scheme 2.12A, comparison of the crude reaction mixture ^{1}H NMR spectra shows that only the signals at 5.9 ppm belonging to the proton at C-5 display a baseline separation, necessary to properly determine the diastereomeric ratio.

To further confirm the assigned stereochemistry via NOESY measurements, the flexible open chain system was transformed into a closed ring system. For this, hydrozirconation product **94** (entry 8) was reacted with NaH in DMF at 100 °C to deprotonate the OH-group and enable an intramolecular attack on the Boc group (scheme 2.12C). NOESY measurements on the resulting carbamate mixture revealed a correlation between the hydrogens at C-2 and C-3 only for the minor diastereomer. Since the correlation is supposed to be much stronger for the (*R*)-isomer, it concedes well with the stereochemical assignments.

2.2.3 Alkynilation of serine derivatives

A different approach to the sphingoid base is the direct addition of alkynes to serine derivatives, possible by deprotonation of the terminal carbon with a strong base such as *n*-BuLi. The lithiated alkyne then adds to the carbonyl group of the serine derivative, elongating the carbon chain. The internal alkyne moiety has to be reduced to the alkene in a second separate step to access the allylic moiety, either following directly the addition reaction or at a later stage in the synthesis. Although longer in the step-count than the hydrometallation approach, this allows for a flexible synthetic strategy, since alkynes are known to be more stable to oxidative or acidic conditions than the respective alkenes.[117,118]

Thus, alkyne **79** was deprotonated with *n*-BuLi and added to the Weinreb amide **89** in 68 % yield (scheme 2.13B). With the ketone in hand, a stereoselective reduction at C-3 is performed next. The transition states of scheme 2.10B can be applied accordingly. Since the hydride is the nucleophilic species here, the resulting stereochemistry is inverted compared to the addition reactions to Garner's aldehyde: Accordingly, the Felkin-Anh-controlled reduction by DIBAL-H was performed and **99** was obtained in



Scheme 2.12: A) ^{1}H-NMR spectra comparison of select hydrozirconation conditions; B) overlayed NOESY and COSY spectra of derivative mixture **96**; C) derivatization to the carbamate **96** to gain more insight into the stereochemistry.

48 % yield. However, the Red-Al® reduction to alkene **94** resulted in decomposition of the alkyne.

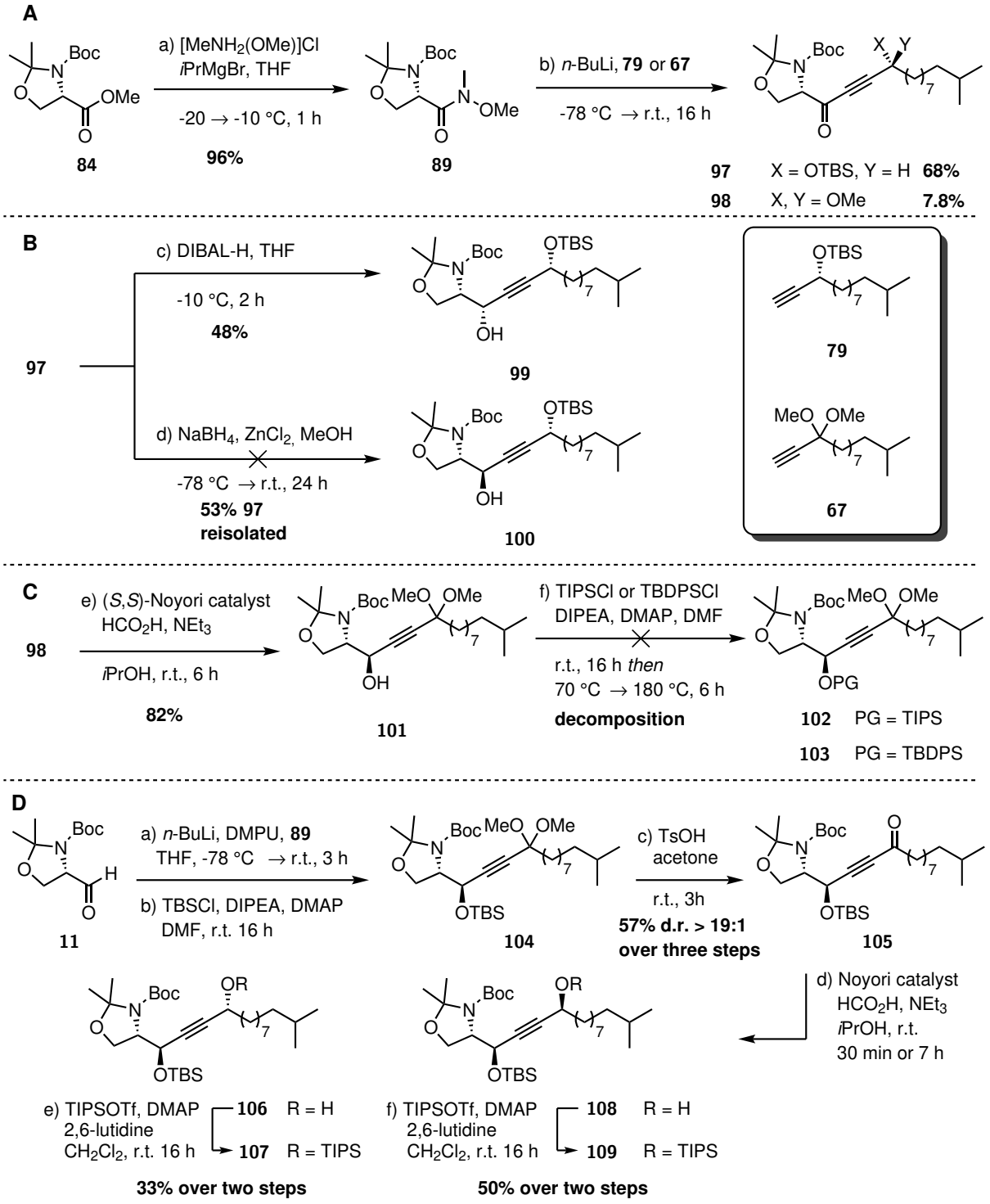
The chelation controlled hydride attack yields the (*3R*)-isomer, yet, only starting material was recovered in the reduction using $ZnBH_4$.

In a different approach, alkyne **67** was added to Weinreb amide **89** in 7.8 % yield and the alcohol **101** was obtained by a Noyori asymmetric transfer hydrogenation in 82 % yield (scheme 2.13). Here the introduction of the TIPS and TBDPS groups was envisaged, however, during the protection reactions no progress was observed at room temperature and only decomposition occurred when the reaction mixture was heated. A reason may be the steric hindrance provided by the Boc-group, which slows down the attack of the hydroxy group on the silyl chlorides. Upon heating, the labile ketal moiety may be cleaved and undergoes side reactions.

To introduce a protecting group at C-3, the smaller TBS-group was thus chosen. To additionally shorten the reaction sequence, alkyne **67** was added directly to Garner's aldehyde **11** in a diastereoselective manner (scheme 2.13). Subsequent protection of the secondary alcohol with TBSCl and deprotection of the ketone afforded **105** in 55 % yield over three steps. Noyori's asymmetric hydrogen transfer protocol was applied again to reduce the ketone group. While a matched effect was observed for the reduction with the (*S*,*S*) enantiomer of the ligand yielding alcohol **108** within 30 min at room temperature in 63 %, a mismatched effect was observed for the (*R*,*R*)-enantiomer resulting in only 37 % yield after 7 h using a higher catalyst loading.

Next, the propargylic alcohols at C-6 were TIPS-protected using TIPSOTf and 2,6-lutidine in 80 – 88 % yield. Again, the steric influence of the Boc-group became noticeable in the unusually long reaction times for silyl protection with silyl triflates.

The (*3R*) congener **100** was obtained by reacting Garner's aldehyde **11** with alkyne **79** in a similar fashion. After Red-Al®-reduction of the alkyne, the diastereomeric ratio was determined to be 18/1 by comparing the ^{1}H-NMR signals at C-5, which corresponds with literature reports.[105] However, the Red-Al® reduction of **99** to **94** resulted in decomposition of the alkyne.

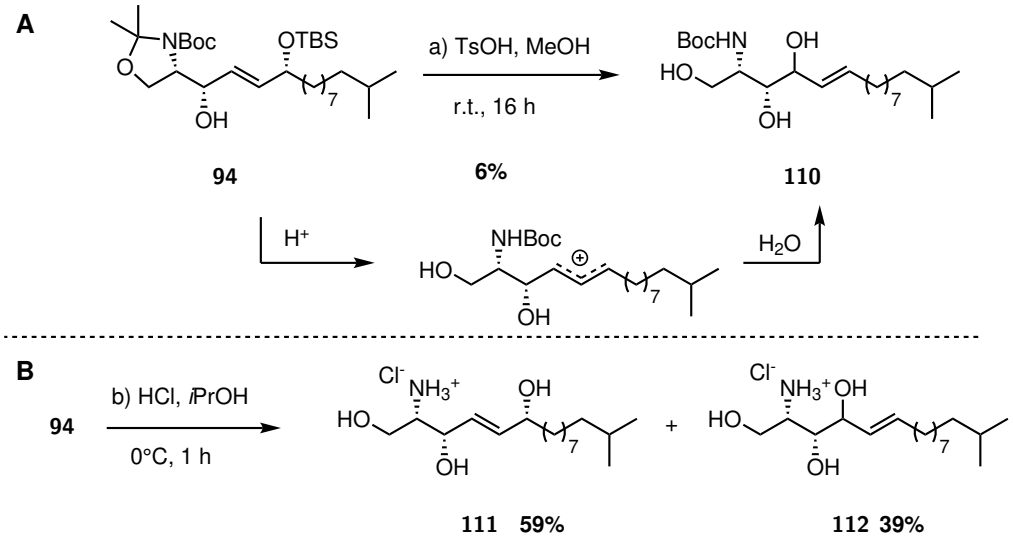


Scheme 2.13: A) Synthesis of ketones **97** and **98**; B) diastereoselective reduction at C-3; C) reduction and protection at C-3; D) synthesis of protected propargylic alcohols **107** and **109**.

2.2.4 Boc-deprotection strategies

The synthesis was then continued with the double deprotection of the acetonide and Boc-group to generate the free amines suitable for acylation reactions. Poor yields, loss of all protecting groups prior to the Boc-group, as well as isomerization of the C6-OH group were observed when acidic deprotection conditions (TsOH) were used (scheme 2.14A).[119] The formation of isomers can be explained by an elimination-addition mechanism, possibly influenced by hydrogen bonding to direct the attack of water to C-4. Non-isomerized amine **111** was obtained with stronger HCl and shorter reaction times at lower

temperature,[91,120] indicating that the isomerization process occurs over time in the acidic environment. But even under optimized conditions, the side product **112** was formed, and the silylether was cleaved, requiring reprotection steps (scheme 2.14B).



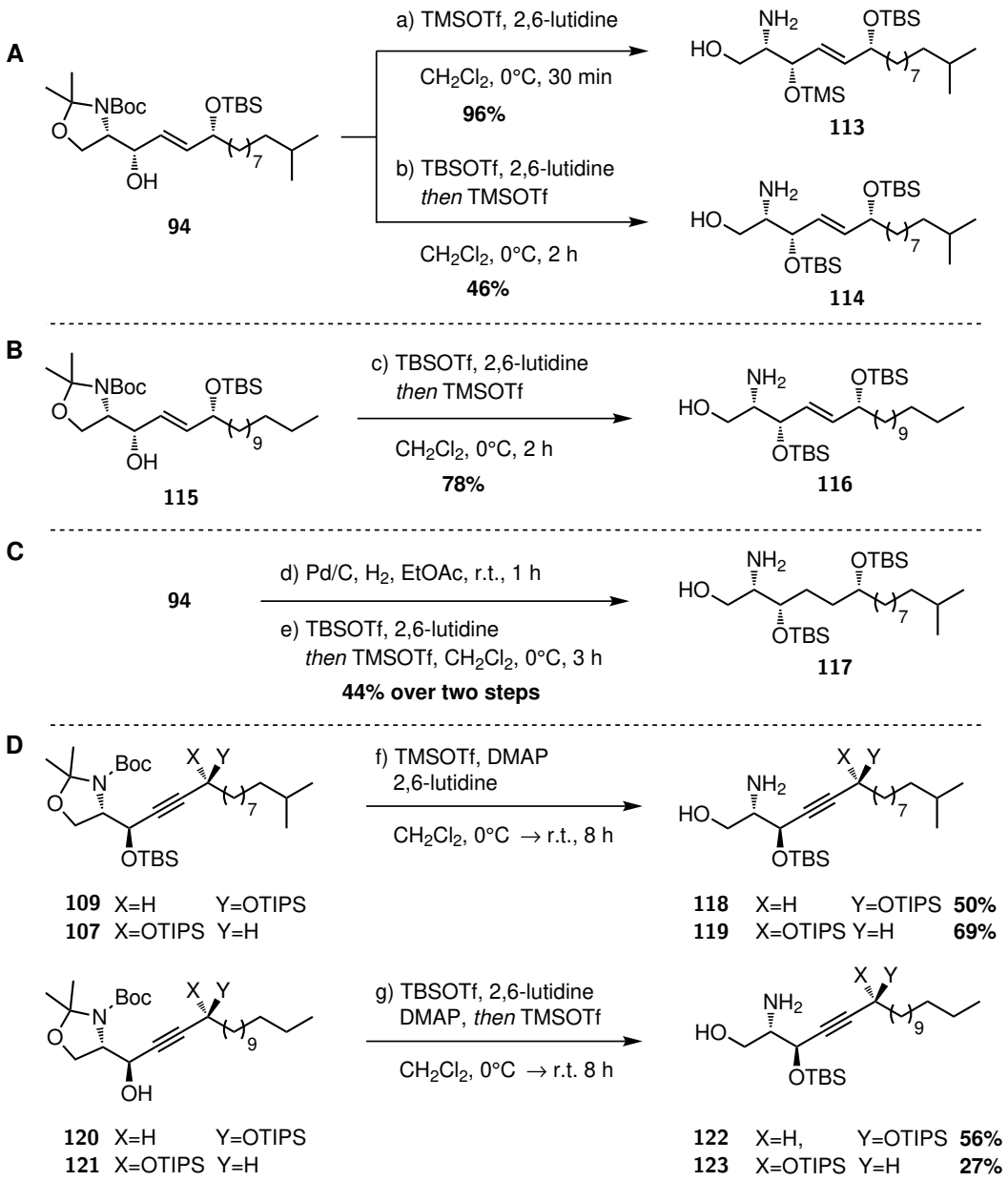
Scheme 2.14: Deprotection of **94** with Brønsted acids.

Based on literature reports that described the selective trans-esterification of *tert*-butyl esters and –carbamates to their respective silyl analogues by strong silylation reagents,[121] silylating conditions were applied to **94** and furnished amine **113** in 96 % yield (scheme 2.15A). With TMS being a rather labile protecting group, the reaction conditions were altered. Thus the alcohol was TBS-protected with a single equivalent of TBSOTf first, then Boc and acetonide protecting groups were removed with an excess of the stronger TMSOTf, delivering amines **114** and **116** in 46 – 78 %.

Hydrogenation of **94** followed by Boc-deprotection provided **117** in 44 % yield over two steps, giving access to derivatives with single bonds for SAR-studies (scheme 2.15C). It must be noted, that due to decreased reactivity, the TBS-protection step required longer reaction times compared to the allylic congeners.

To follow up the route with the alkyne moiety as well, propargylic alcohols **107** and **109** were similarly Boc-deprotected. Since both secondary alcohols are already silyl-protected, Boc and acetonide deprotection was carried out using only TMSOTf, and the free amines **118** and **119** were obtained in 50 – 69 % yields (scheme 2.15D). The linear congeners **120** and **121** do not contain the second silyl group at C-3, thus they were submitted to silylation reaction conditions with TBSOTf and TMSOTf. The free amines were then obtained in 27 – 56 % yield (scheme 2.15D).

Overall, eight free amines were readily available using this deprotection sequence with silyl triflates in 27 – 96 % yield.



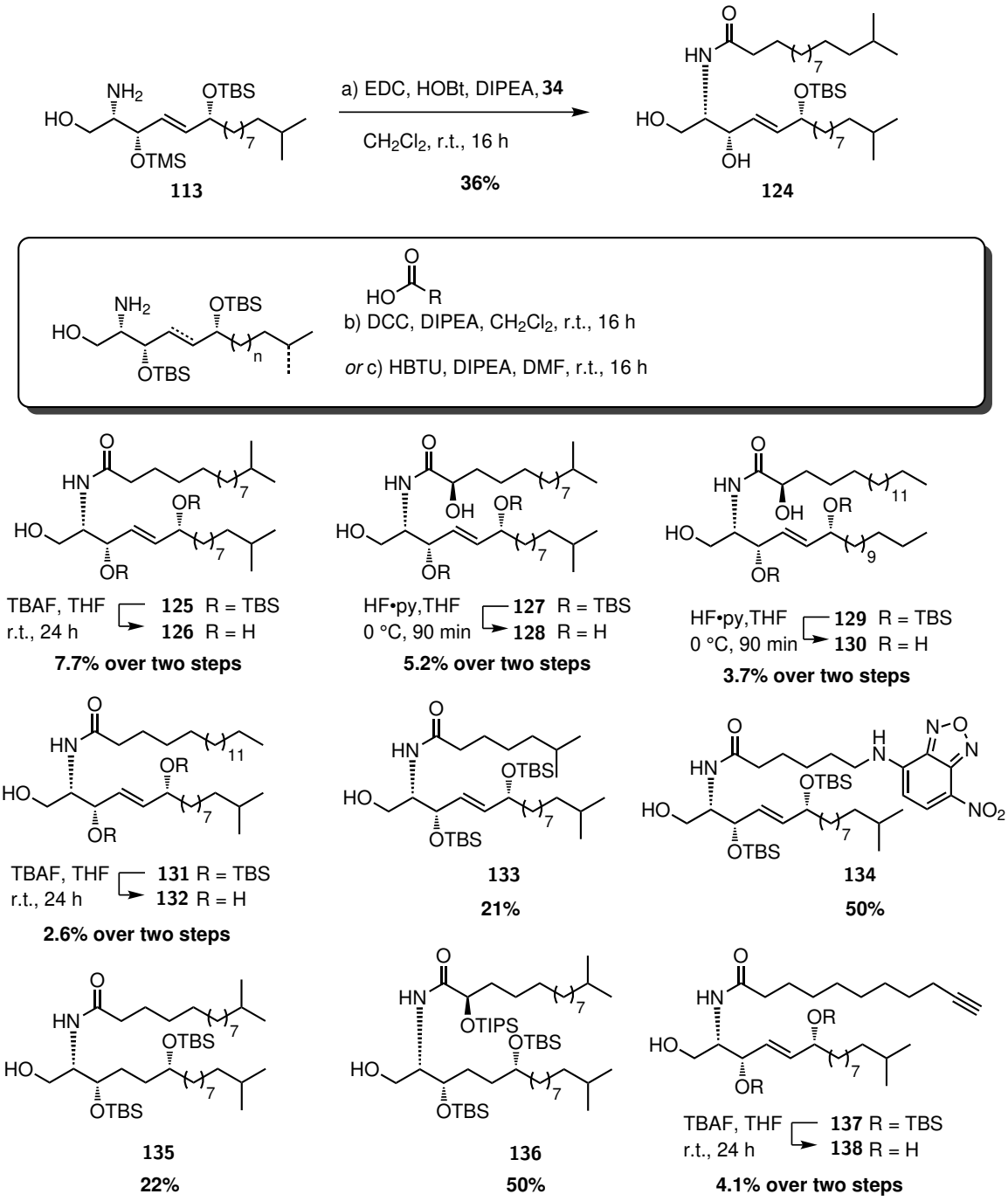
Scheme 2.15: A), B) Boc-Deprotection of **94** and **115** with silyl triflates; C) synthesis of hydrogenated capnine base **117**; D) Boc-deprotection of **107**, **109**, **121** and **123**.

2.2.5 Synthesis of unnatural ceramides

With access to sphingoid bases with their respective diastereomers at C-3 and C-6 as well as various fatty acids, the combination thereof to ceramides was investigated next.

Therefore, TMS-protected amine **113** was submitted to peptide coupling conditions with EDC, HOBt and carboxylic acid **34** in preliminary attempts. The amide was obtained in 36 % yield and the TMS-group was cleaved during the reaction. Investigations using amines bearing the more stable TBS-group (**114** and **115**) indeed yielded the desired amides without deprotection in vicinity of the allylic system.

To further improve the yields, a condition screening was performed and revealed either DCC and DIPEA in CH_2Cl_2 or HBTU and DIPEA in DMF to be more optimal coupling conditions. Thus, in total nine protected amides with (*3S*)-configuration were synthesized in 21 – 50 % yield, among which four were deprotected using TBAF/THF or HF·pyridine complex. Here, emphasis was put on variation in the fatty acid part (branched and linear, different length, additional hydroxylation) while retaining the

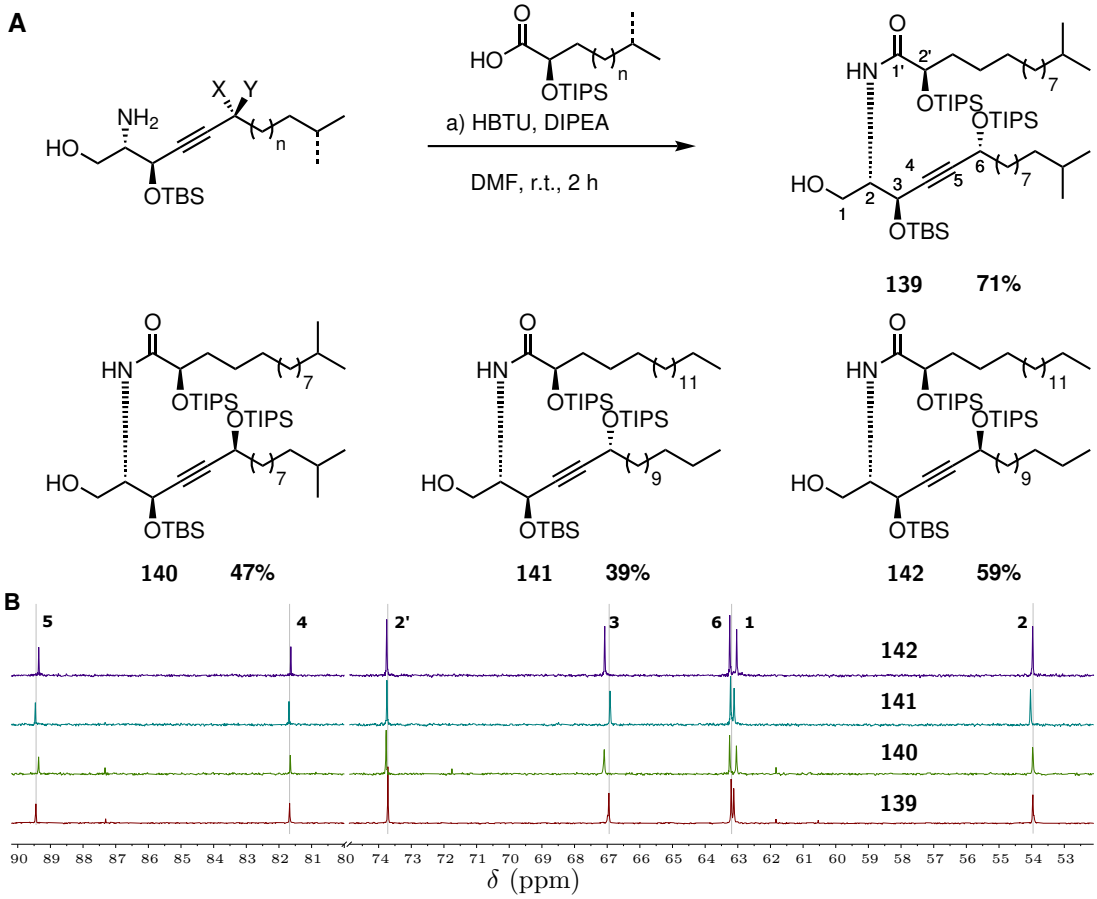


Scheme 2.16: Synthesis of unnatural ceramides.

stereochemistry in the sphingoid base. To introduce variety here, select acids were combined with the linear amine **116** and hydrogenated congener **117**.

As further investigations for the biological activity were envisaged, the introduction of a fluorescent label was pursued. 6-NBD-hexanoic acid-modified sphingosine was used to visualize the Golgi apparatus in living cells[122] and was integrated into derivative **134**. Furthermore, the preparation of **138** bearing a terminal alkyne moiety allows for the introduction of functional tags within living organisms using modified click reaction conditions.[123]

For (*3R*)-ceramides, the free propargylic amines **118**, **119**, **122** and **123** were coupled with branched fatty acid **61** or linear acid **59** to obtain amides **139**, **140**, **141** and **142** in 39 – 71 % yields. Only small differences were observed when comparing their NMR-spectra (scheme 2.17B). The most pronounced



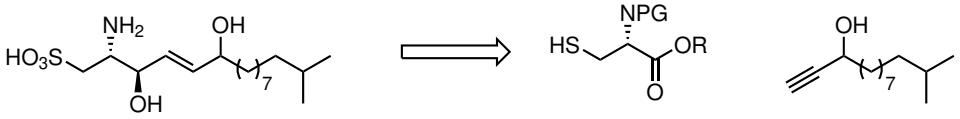
Scheme 2.17: A) Synthesis of alkyne amides **139**, **140**, **141** and **142**; B) comparison of ^{13}C-NMRs thereof.

shift in the ^{13}C-NMR-spectrum is observed for carbons in position 5 (low field shift for (*R*)-isomers in comparison) and 1 (low field shift for (*R*)-isomers), a minor influence is visible for the carbons in positions 6 (high field shift for (*R*)-isomers), 4 (low field shift for (*R*)-isomers) and 3 (high field shift for (*R*)-isomers). Although the stereochemistry changes only in the 6-position for all four amides, conformational changes in the alkyl chain seem to have a greater influence on the electronic environment of the polar head than on the stereocenter itself.

Summarizing, 14 ceramide derivatives were synthesized using the Garner's aldehyde approach in 8 to 10 synthetic steps (longest linear sequence) from commercially available starting material.NMR comparison of **139**, **140**, **141** and **142** revealed only minor differences, with the most pronounced shifts not at the epimeric center, but rather at the adjacent atoms.

2.3 Investigation of the "cysteine strategy"

As the synthesis of ceramides has been accomplished, endeavours were undertaken towards the synthesis of sulfonolipids as well. The straight forward way is to apply the established conditions using cysteine instead of serine. Here the readily oxidized thiol moiety is included in the head group from the start, allowing rapid access to sulfonolipids.[124] However, literature reports on addition reactions to the carbonyl group of cysteine derivatives are scarce and indicate low diastereoselectivity, if an aldehyde is used.[125] This may require a detour *via* the ketone functionality, having again negative impact on the overall step count.

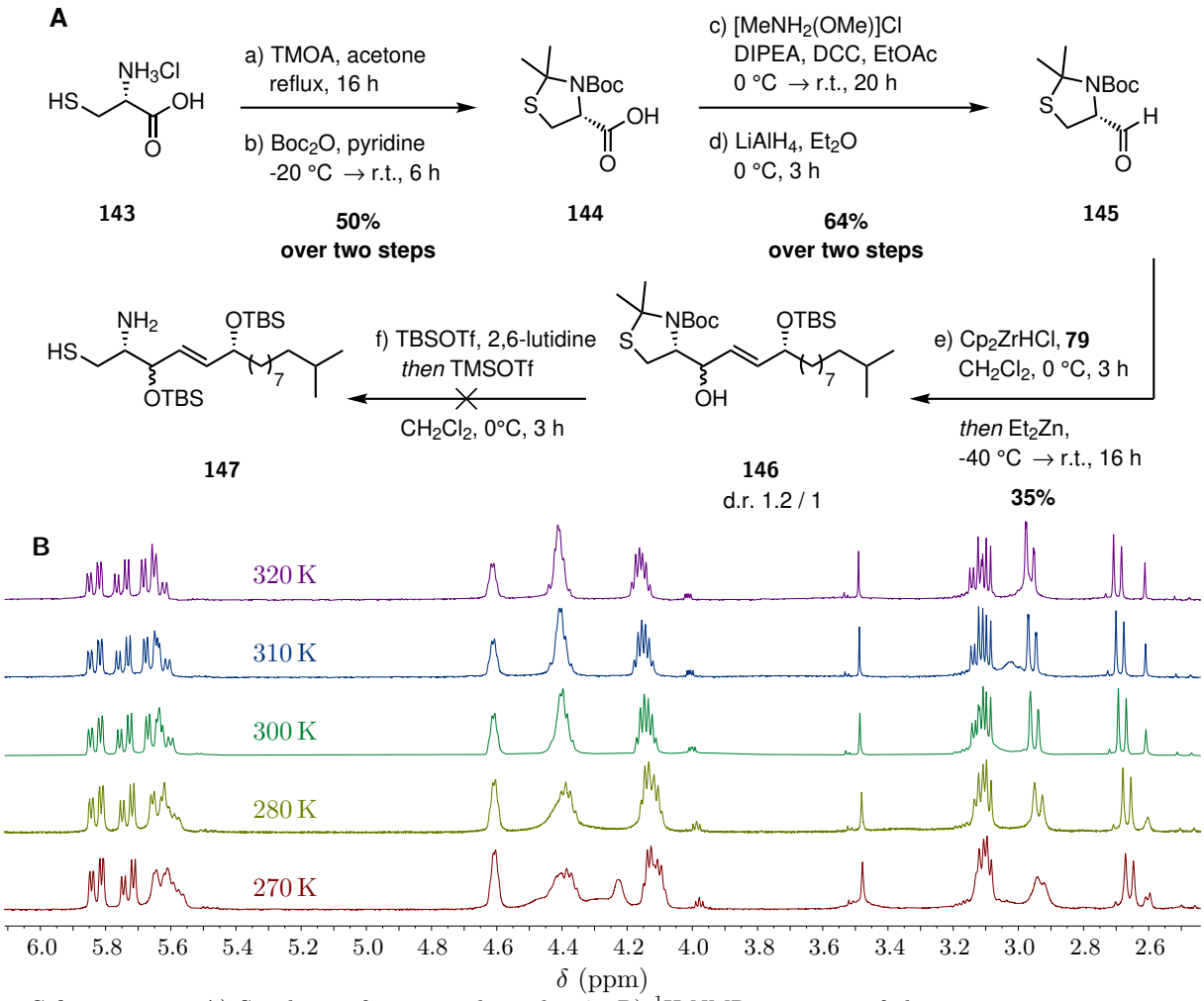


Scheme 2.18: Retrosynthetic approach to sulfonolipids starting from cysteine derivatives.

Literature known aldehyde **145** was obtained in four steps from cysteine hydrochloride **143** in 35 % yield compared to the 41 % reported yield (scheme 2.19A).[126] To elongate the carbon chain, alkyne **79** was used in a hydrozirconation reaction to yield the desired addition product **146** in a diastereomeric ratio of 1.2/1.0. NMR analysis revealed the formation of pseudodiastereomers caused by a slow inversion of the nitrogen lone pair, which can be resolved by measuring the spectrum at temperatures other than r.t. (scheme 2.19B).[127] The best resolved peaks were obtained at 320 K and overall the effect is less noticeable than for the serine derivative **79**. Again only the peaks at C-5 show a baseline separation in the ^{1}H-NMR, which is required to determine the diastereomeric ratio.

Proceeding in the synthesis, the diastereomeric mixture was then subjected to Boc-deprotection conditions using silyl triflates,[121] while keeping in mind, that harsh conditions are usually required for *S*,*O*-acetonide deprotection reactions.[128] Despite observations of Boc-deprotection via LC-MS, no product was isolated. Other reported conditions (e.g., the use of Brønsted acids) were not tested, as the silyl protecting group is cleaved more easily under acidic conditions than the Boc-group (see also section 2.2.4). The expected isomerization as well as additional reprotection steps made this approach cumbersome lead to the abandonment of this route.

A different protecting group strategy may solve the discovered problems, but since more general synthetic strategies towards sulfonolipids have been laid out (section 1.3), these were pursued first.



Scheme 2.19: A) Synthesis of cysteine derived **147**; B) ^{1}H-NMR spectrum of the **146** reaction mixture, recorded at different temperatures.

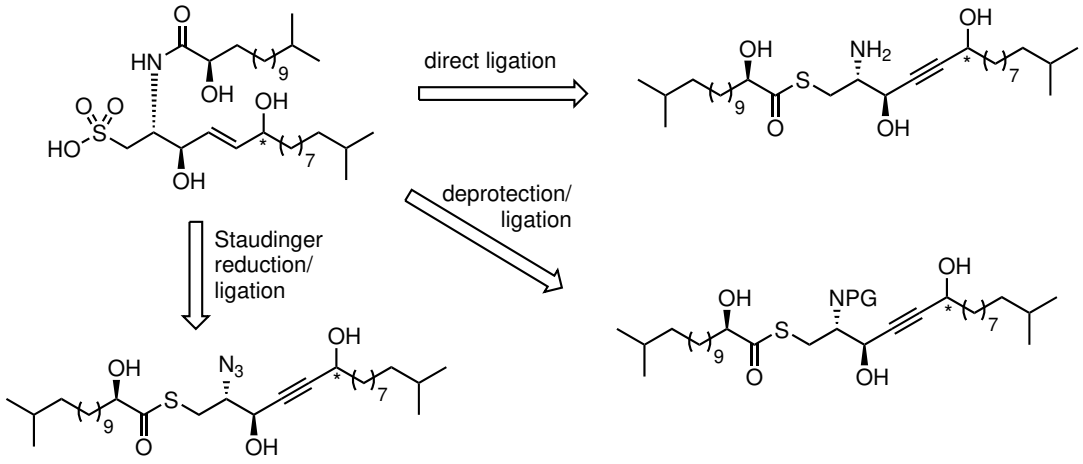
2.4 Studies towards the "thioligation strategy"

The second strategy for sulfonolipid formation is based on a ligation of the acyl group from sulfur to nitrogen (scheme 1.4). This methodology is widespread in peptide synthesis in the form of native chemical ligation to combine smaller peptides into larger proteins.[64] This opens three possible paths for the synthesis of sulfonolipids (scheme 2.20): (1) the direct ligation of the acyl group to a free amine, (2) the ligation after deprotection of the amine[65] or (3) the ligation after a Staudinger reduction of an azide group to the amine,[64,129] which can be regarded as a special case of the deprotection/ligation sequence. All these paths require an oxidation step after the ligation.

2.4.1 Reactions using short chain test substrates

First, aldehyde **11** was reacted with hex-1-yne and *n*-BuLi in the presence of HMPA to **148** in 47 % yield (scheme 2.21B). The determination of the diastereomeric ratio proved difficult because the rotamer formation is more pronounced in this molecule than in **79** or **146** and pseudodiastereomers are detected even at high temperatures. Furthermore, the separated signals of the double bond region are missing, and no baseline separation was observed for the other signals.

To introduce a protecting group at C-3, TBS and TIPS were chosen so that their reactivity could be compared during the following steps. Thus, reaction of propargylic alcohol **148** with TBSOTf or TIPSOTf afforded the respective silyl ether in 60 – 72 % yield.

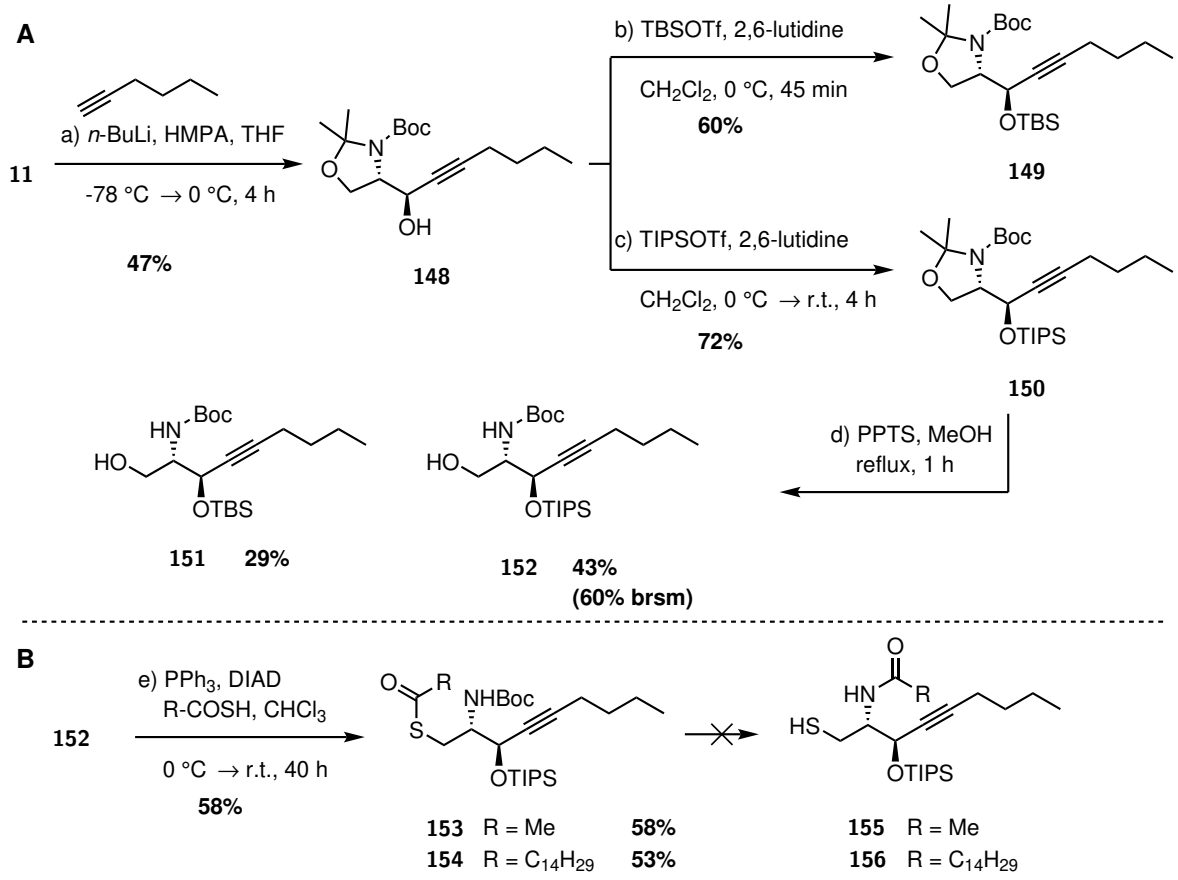


Scheme 2.20: Approaches using the thioligation reaction.

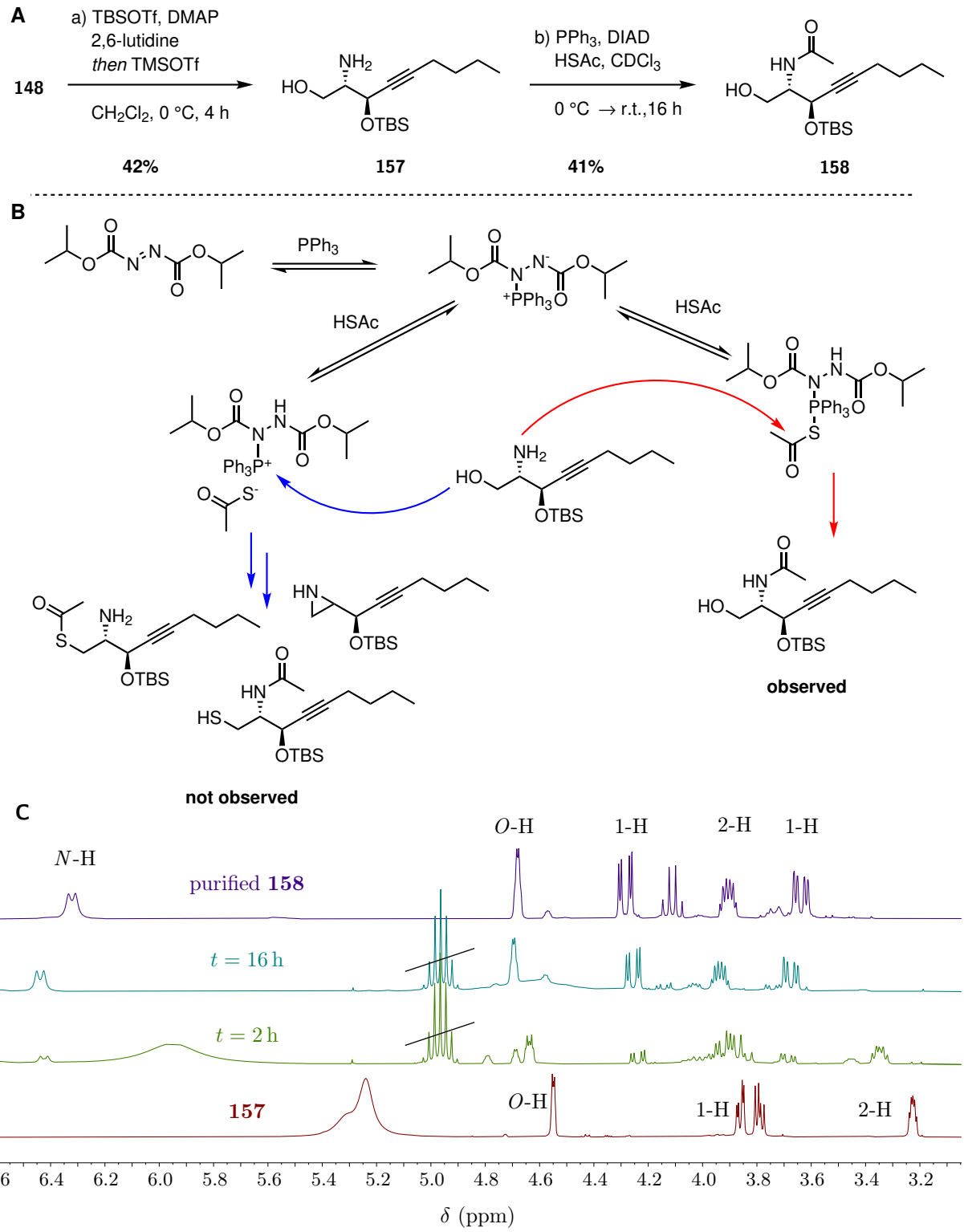
To introduce thioacids at C-1 *via* substitution, the selective acetonide deprotection in the presence of silyl ethers and the Boc-group was investigated next. Due to poor solubility, the reaction with $BiBr_3$ in MeCN[130] or $CuCl_2 \cdot 2\,H_2O$ in MeCN[131] as well as the reaction in 80 % aqueous AcOH[132] resulted only in recovery of the starting material. Treatment with sulfonic acids in MeOH, however, resulted in acetonide deprotection. The best results were achieved when the acetonides **149** and **150** were reacted with PPTS in refluxing MeOH for 1 h[133] and the reaction quenched before completion to prevent the competing silyl deprotection (scheme 2.21B).

With the free primary alcohol **152** in hand, Mitsunobu reaction conditions were applied to introduce HSAc and thioacid **SI-21**, available in a single step from carboxylic acid **34**. Thioesters **153** and **154** were thus available to test the ligation reaction upon Boc-cleavage (scheme 2.21B); however, no reaction progress was observed for the reaction with silyl triflates.[134] Addition of PhSH and heating of the mixture resulted in the consumption of the thioester,[135,136] but only to complex mixtures with traces of the product mass detectable in the LC-MS for **153**. Acidic conditions were neglected to avoid desilylation and isomerization as side reactions.

As Boc deprotection of thioesters proved troublesome, the protecting group was supposed to be removed prior to thioester introduction. Thus propargylic alcohol **148** was TBS protected as well as Boc and acetonide deprotected, which delivered amine **157** in a single reaction with 42 % yield (scheme 2.22A). The free amine was then subjected to Mitsunobu conditions and surprisingly amide **158** was formed in 41 % yield as the sole isolated product. The reaction was then performed on small scale to better monitor the reaction pathway (scheme 2.22B). As expected, a big shift is observed for the proton at C-2. The peak of the diastereotopic protons at C-1 on the other hand shows a splitting rather than the expected shift to higher fields from thiol introduction. Additionally, the peak for the NH-proton at 6.5 ppm emerges in the same ratio as the signals for the educt disappear, which overall indicates a mechanism that works via a direct attack of the free amino group on activated thioacetate (red path in scheme 2.22B) rather than intermediary thiol formation. This contrasts the Mitsunobu reaction mechanism, where the free OH group adds to the activated complex to form a good leaving group, which is then attacked by nucleophiles (blue path in scheme 2.22B). It is likely, that the addition of more equivalents of PPh_3 and DIAD together with HSAc after amide bond formation leads to a one pot peptide coupling/Mitsunobu reaction. However the big excess of reagents is a major drawback, as the thiocarboxylic acids have to be synthesized in several steps by themselves and the atom economy also suffers greatly. Hence, this reaction was not investigated further.



Scheme 2.21: Synthesis of short chain substrates **153** and **155** to investigate the thioligation reaction.



Scheme 2.22: Mitsunobu reaction of free amine **157**.

Table 2.2: Tested conditions for the thioligation of **162**

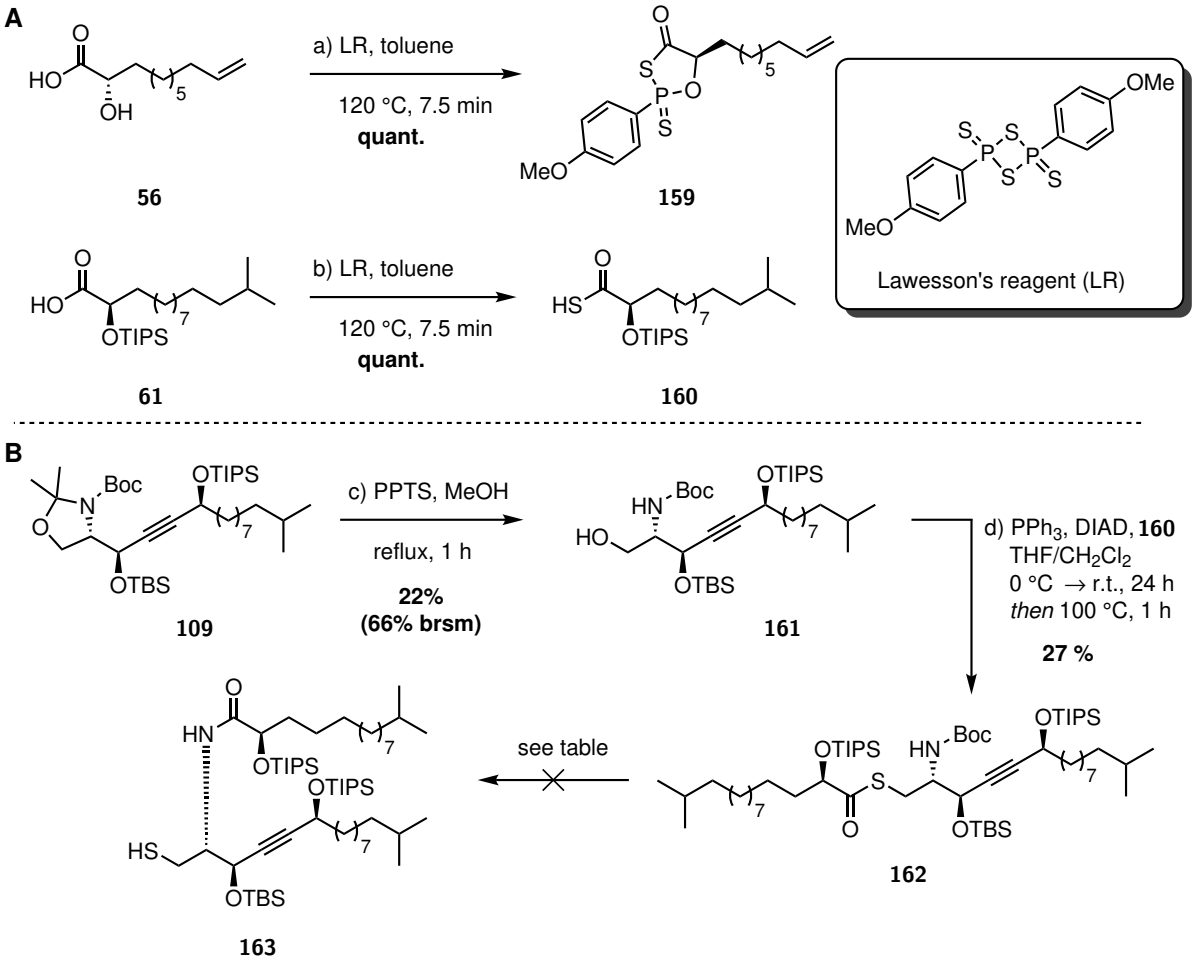
Entry	Reagents	Result
1	TMSOTf, 2.6-lutidine, neat, 0 °C→ r.t., 16 h	n.r.
2	TMSOTf, 2,6-lutidine, DMF, 0 °C→ r.t., 16 h	n.r.
3	TMSOTf, 2,6-lutidine, neat, 0 °C, 2 h	complex mixture
4	TBSOTf, 2,6-lutidine, neat, 0 °C, 2 h	complex mixture
5	TIPSOTf, 2,6-lutidine, neat, 0 °C, 2 h	complex mixture
6	DMPU, 180 °C, 40 min	n.r.
7	PhSH, toluene/$CHCl_3$ 5/1, r.t. → 150 °C, 20 min	n.r.
8	PhSH, toluene/$CHCl_3$ 5/1, 150 °C, 1 h	n.r.
9	AcCl, EtOH, EtOAc, r.t., 16 h	silyl deprotection only

2.4.2 Reactions with propargylic ethers

Despite the mediocre results obtained for the shorter chain analogue, the thioligation was tested with a longer chain propargylic alcohol, bearing the stereocenter at C-6. Therefore, alkyne **67** was added diastereoselectively to Garner's aldehyde **11** (scheme 2.13B). Subsequent protection of the secondary alcohol with TBSCl and deprotection of the ketone afforded **105** in 55 % yield over three steps. Noyori's asymmetric hydrogen transfer protocol was applied again to reduce the ketone group. While a matched effect was observed for the (*S*,*S*) enantiomer of the ligand yielding alcohol **108** within 30 min at room temperature in 63 %, a mismatched effect was observed for the (*R*,*R*)-enantiomer resulting in only 37 % yield after 7 h. Next, the propargylic alcohols were TIPS-protected using TIPSOTf and 2,6-lutidine in 33 – 50 % yield over two steps.

Similar to **SI-21**, the synthesis of α-OH-thiocarboxylic acids was achieved by the reaction of carboxylic acids with Lawesson's reagent (scheme 2.23). For fully deprotected acid **56**, the addition product **159** was isolated in quantitative yield, clearly identified by the quadruple set of signals in the ^{13}C-NMR associated with the five-membered ring.[137] For TIPS-protected carboxylic acid **61**, the reaction yielded the thiocarboxylic acid **160** in quantitative yield. Alternative methods to access the thiocarboxylic acid were tested (activation with IBCF or CDI and coupling with NaSH)[138,139] and promising results were obtained for small scale test reactions, but the scale up remained without success, thus the reaction with Lawesson's reagent was maintained as the method of choice. With thiocarboxylic acid **160** and free alcohol **161** (available via deprotection of **109** with PPTS in refluxing MeOH) at hand, the Mitsunobu reaction conditions were applied to form the thioester **162** in poor yield (27 %). No increase in yield was obtained by varying the temperature, solvent, or by the addition of an external base.[140] This might be due to the α-substitution in the thioacid, since the Mitsunobu reaction with an unsubstituted acid gave higher yields (see scheme 2.21).

The Boc-deprotection of thioester **162** was tested using an excess of silyl triflates (entries 1–5 in table 2.2). No reaction progress was observed for small excess of silylating reagents and an increase to large excess rapidly lead to the formation of a complex reaction mixture. It can be speculated that the bulky silyl groups and alkyl chains surround the Boc-group and make it inaccessible to the silylating agents. The application of heat only (entry 6) should trigger thermal decomposition of the *tert*-Butyl carbamate independent from the steric surrounding. But neither heat alone nor in combination with PhSH (entries 7–8) as cation scavenger resulted in reaction progress. The use of protic acids such as HCl in EtOAc (entry 9) only resulted in silyl-deprotection without cleaving the Boc-group (see also section 2.2.4). Since the silyl ethers were deemed crucial for the oxidation step, no further attempts using Brønsted acids were undertaken.

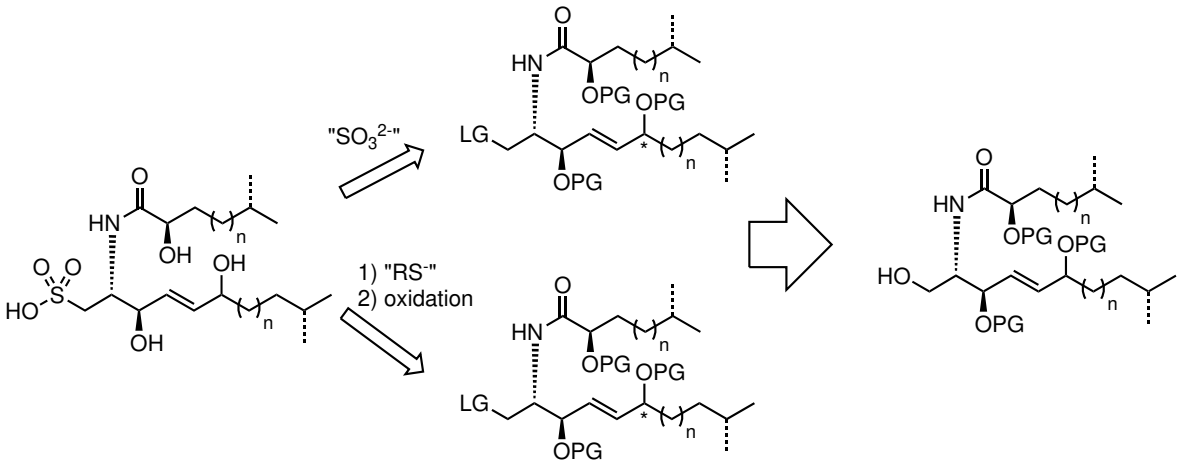


Scheme 2.23: Synthesis and thioligation reaction of **162**.

Summarizing, the low yields in the selective acetonide deprotection step and in the Mitsunobu reaction introducing the thioacid severely impede a successful scale-up of the thioligation pathway. Moreover, the key step of the reaction, the thioligation reaction itself, remained without product formation. And only amide bond formation without thiol introduction was observed when the free amine was used. Thus, the next strategy, the late-stage approach was investigated further.

2.5 Synthesis of sulfonic acids — "late stage strategy"

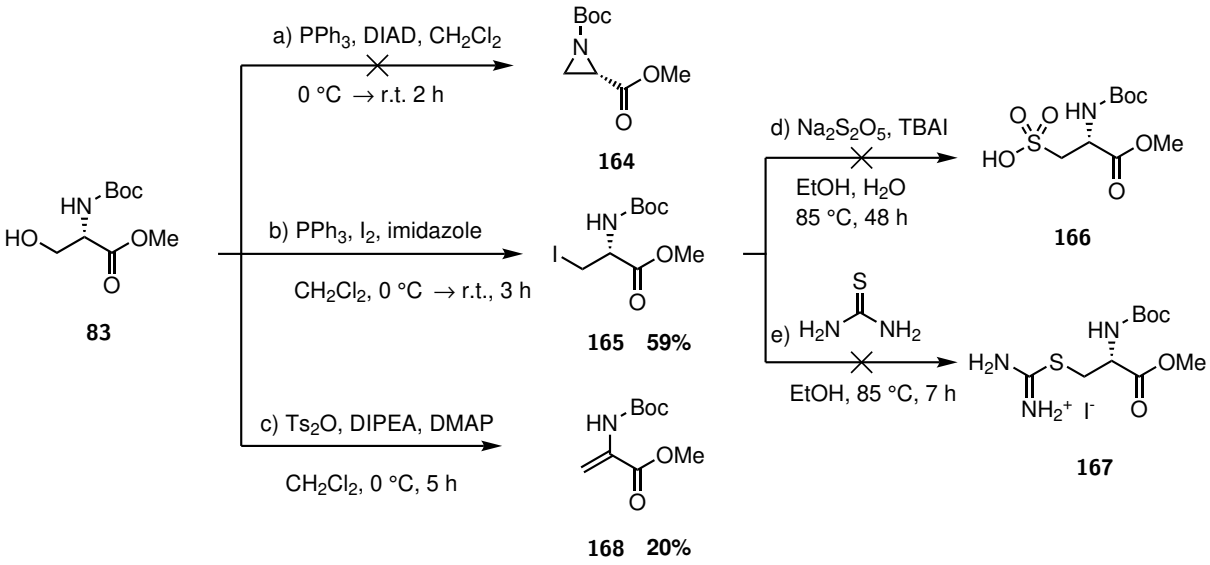
Starting off with the late stage strategy, the sulfonic acid introduction is set in a late stage of the synthesis by a substitution reaction of the alcohol at C-1 either by substitution of the ceramide C-1 OH group either by (1) a sulfite salt or sulfonate or (2) a thiol followed by oxidation (scheme 2.24). As reported in the literature, the low nucleophilicity of sulfite salts usually results in low yields for these kinds of substitutions.[37] As such, the detour of replacing leaving groups with sulfide sources (isothiocyanates,[141,142] sulfide salts,[143] thiourea,[144,145] thiocarboxylic acid salts[146] or other thiols[147]) is widespread in the literature. A second, separate oxidation step may provide the sulfonic acid in an overall higher yield.[148]



Scheme 2.24: Overview of synthetic approaches to sulfonic acid introduction in sulfonolipid synthesis.

2.5.1 Synthesis of cysteic acid derivatives

For preliminary test reactions, commercially available serine derivative **83** was selected and the impact of different leaving groups was examined. As such, the work started with the investigation of aziridine formation, a putative intermediate in all substitution reactions en route to sulfonolipids.[61] Similarly to epoxides, these three-membered rings open to release ring strain and thus serve as leaving groups as well. Their formation is induced by intramolecular substitution in an α amino, β leaving group system by the nitrogen. Therefore Mitsunobu reaction conditions were applied to generate the aziridine from **83** (scheme 2.25).[149] No product was isolated and thus the leaving groups I^- and OTs^- were employed. Iodination with PPh_3, imidazole and I_2 furnished ester **165** as well as elimination product **168**.[150,151] Tosylation of **83** using Ts_2O and DIPEA afforded only the elimination product **168**, probably due to the use of more basic reaction conditions, which prompt the elimination reaction instead of the substitution. Mechanistically, proton abstraction at the acidic α position of the carbonyl group easily leads to extrusion of the leaving group at the β-position according to a $E1_{cb}$-like mechanism No aziridine formation was observed in these reactions, findings which were further corroborated by P. Stephan in a more detailed study.[152] Nevertheless, the iodinated compound **165** was subjected to substitution reaction conditions with thiourea or $Na_2S_2O_5$ in refluxing EtOH.[145] However, no product formation was observed, questioning the overall usefulness of serine ester **83** as starting material for sulfonic acid introduction. Thus work continued with the ceramides synthesized in section 2.2.5.



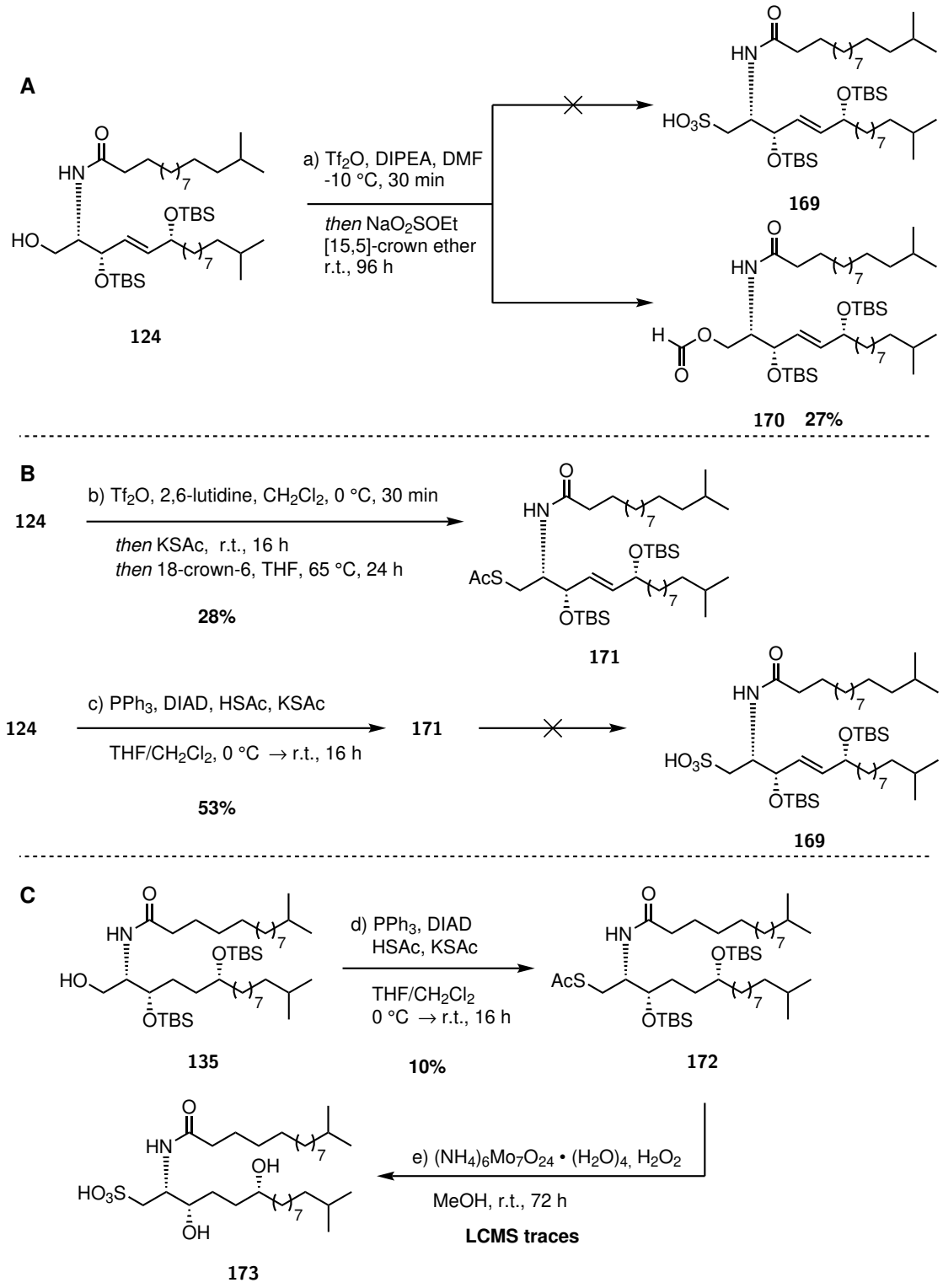
Scheme 2.25: Reactions towards sulfonic acids from commercially available **83**.

2.5.2 Synthesis of (*3S*)-OH sulfonolipids

As such, the direct introduction of the sulfonic acid moiety with sulfite salts was investigated first for ceramide **124** (scheme 2.26A). Since DMF is a polar solvent well suited to dissolve the inorganic salts, it was initially the solvent of choice for the activation with Tf_2O. However, instead of the desired sulfonic acid only formylated product **170** was isolated in 27 % yield. Evidently, Tf_2O activates DMF similarly to $POCl_3$ in the Vilsmeier-Haack-formylation. The reactive species is then attacked by the primary alcohol and leads to formylation. Hence, alternative solvent systems were sought and after screening of several conditions, a CH_2Cl_2/THF mixture was chosen. The use of [15,5] crown ether should further enhance the nucleophilicity of the sulfite salts, but no desired product was formed. NMR-experiments in deuterated pyridine revealed, that the activation most likely is successful, but the substitution does not take place. Thus, the one-pot reaction of activation and subsequent substitution of the alcohol by sulfite salts was abandoned for the introduction of sulfonic acids.

The change to thioacetate as a stronger nucleophile resulted in product formation (scheme 2.26B). With optimized conditions (2,6-lutidine in CH_2Cl_2 to activate the alcohol and KSAc and [18,6] crown ether in refluxing THF to substitute it with SAc^-) yielded the desired protected thiol in 28 % yield. Increased yields (53 %) were obtained with the milder Mitsunobu reaction conditions, which exemplify again the robustness of this reaction and leaving only the oxidation step to complete the synthesis of sulfonic acids.

Extensive investigations were performed with peracids of different strength (*m*-CPBA, H_2O_2 in combination with TFA,[59] formic acid[153–155] or acetic acid[156]) or their respective salts,[157] *in situ*-generated Cl_2,[158] oxone®,[159] or $(NH_4)_6Mo_7O_{24}(H_2O)_4$[157] remained without detectable formation of sulfonic acid (scheme 2.26B). The main problem in these reactions seemed to be the silyl cleavage prior to the oxidation under acidic conditions and complex mixtures were usually obtained. In order to investigate, whether the allylic system itself is problematic under oxidative conditions, for example with epoxide formation and subsequent decomposition,[157] hydrogenated **135** was reacted with HSAc under Mitsunobu conditions to **172** in 9.7 % yield (scheme 2.26C). Testing of a few of the aforementioned conditions finally revealed traces in the LC-MS of the desired sulfonic acid, when $(NH_4)_6Mo_7O_{24}(H_2O)_4$ and H_2O_2 were used in MeOH. Up-scaling and isolation failed, however, and transferring the conditions to the allylic system remained without product formation in the LC-MS. This solidifies the assumption, that the allylic moiety is partially responsible for the low yielding oxidation reactions and needs to be introduced after the



Scheme 2.26: Synthesis of sulfonolipids starting from **124** and **135**.

sulfonic acid is established, for example by stereoselective reduction of a triple bond.

2.5.3 Using the late stage reduction approach to (*3R*)-OH sulfonolipids

With the difficulties to oxidize the thioacetate to the sulfonic acid in section 2.5.2 in mind, the more stable alkyne moiety was envisaged to be used during the crucial oxidation step. This requires then a reduction step of the alkyne to the alkene after the sulfonic acid is formed.

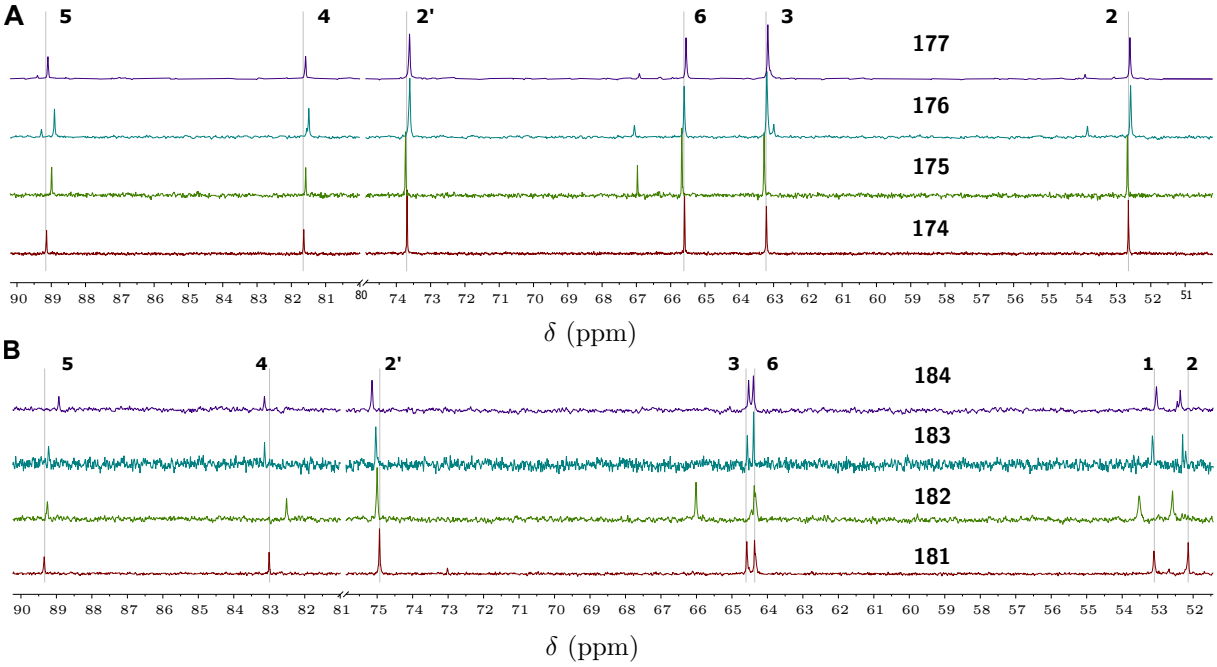
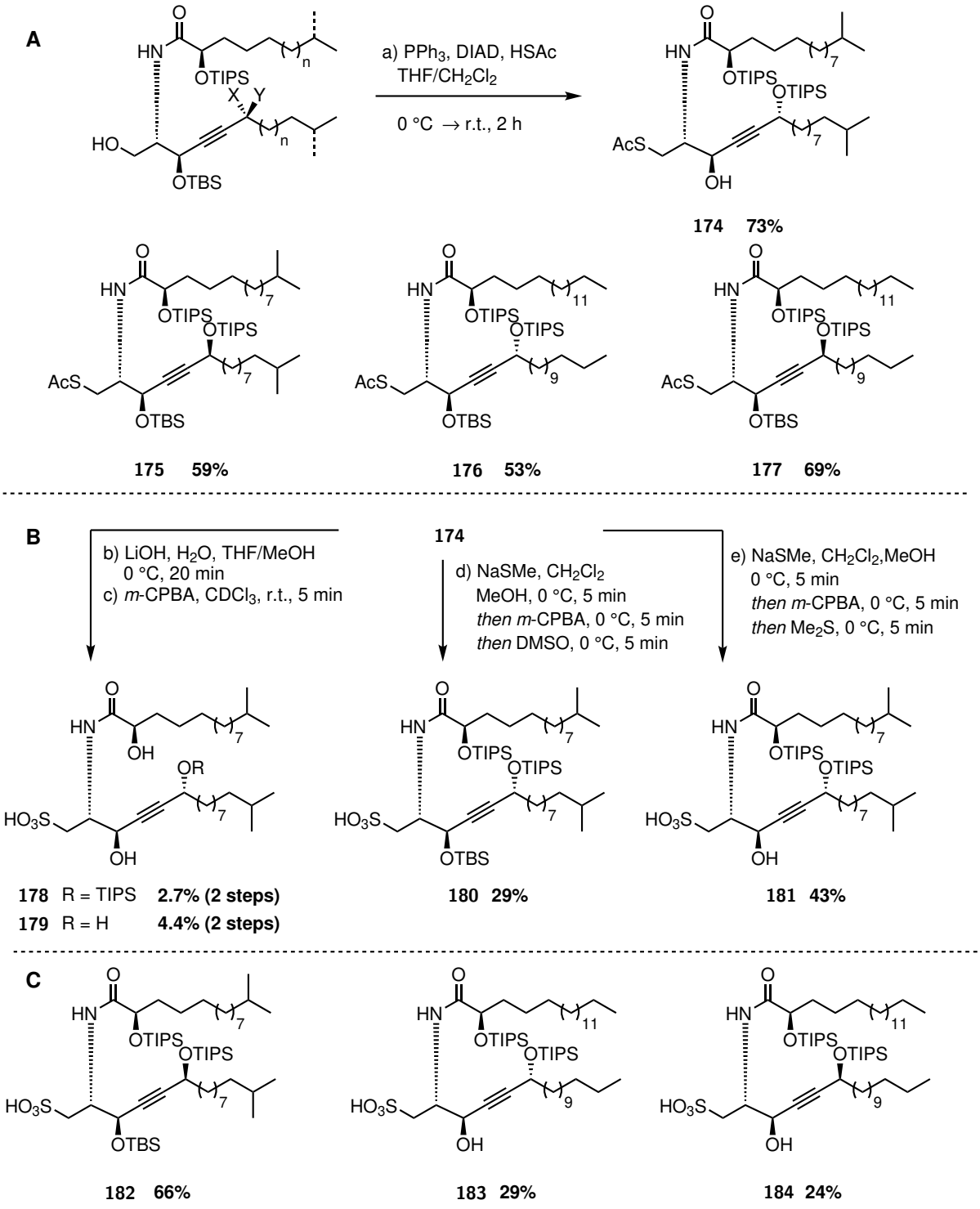


Figure 2.1: Comparison of ^{13}C-NMRs of A) thioacetates **174**, **175**, **176** and **177**; B) sulfonic acids **176**, **181**, **182** and **183**.

As such, the thiol moiety was introduced by Mitsunobu reaction conditions for ceramides **139**, **140**, **141** and **142** in 53 – 69 % yield. With the thioacetates in hand, oxidation conditions with $(NH_4)_6Mo_7O_{24}\cdot(H_2O)_4$ and H_2O_2 were applied; however, no sulfonic acid was formed. Literature research revealed, that a two step procedure may resolve the problem, first deprotection of the thiol followed by a second oxidation step. However, saponification of the thioacetate with LiOH and *in situ* oxidation with peracids (TFA/H_2O_2, FA/H_2O_2) revealed no product formation. Only after isolation of thiol **SI-22** and oxidation with *m*-CPBA in $CDCl_3$, deprotected sulfonic acids **178** and **179** were obtained rather quickly in only 20 min.[124] It seems likely, that non-polar solvents such as CH_2Cl_2or $CHCl_3$ are necessary to properly dissolve the thiol, as *m*-CPBA in MeOH did not yield any product earlier (section 2.5.2). Thus, the reaction conditions were optimized for a one-pot thiol deprotection and oxidation reaction. Deprotection was performed with NaSMe in 5 min at 0 °C, *m*-CPBA was added and the mixture quenched after another 5 min with a reducing agent, e.g. Me_2S. This efficient process yielded sulfonic acids **181**, **182**, **183** and **176** in 24 – 66 %. Under these conditions TBS-deprotection was usually observed, longer reaction times resulted in further deprotection reactions.

The trend with only minor differences in the NMR remains for the thioacetates **174**, **175**, **176** and **177** (figure 2.1). Again, the greatest shifts are not at C-6 itself, but rather at C-5 and C-4, although the high field/low field trend per stereoisomer observed for the amides is only partially detectable here. Where the C-2' and C-6 show a similar pattern to the amide spectra (high field shift for (*R*)-isomers), C-3, C-4 and C-5 show no clear pattern for the pairs of stereoisomers.

Analyzing the ^{13}C-NMR-spectra of the alkyne sulfonic acids, the trend for the respective pairs of diastereomers is gone. Together with overall marginal shifts of less than 0.2 ppm, the lack of a clear tendency prevents an unambiguous assignment of the stereochemistry without reference compounds.



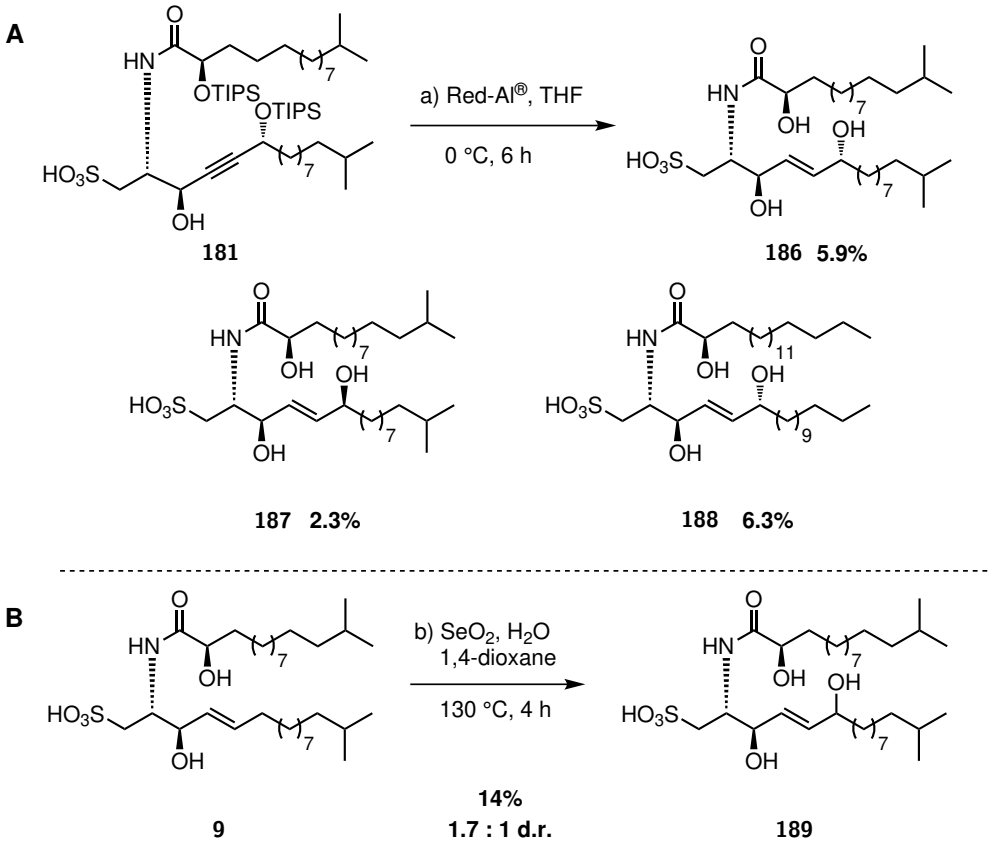
Scheme 2.27: A) Synthesis of thioacetates **174**, **175**, **176** and **177**; B), C) synthesis of sulfonic acids.

2.5.4 The final steps to RIF-2 and comparison of natural product and synthetic compounds

To finalize the synthesis, the alkyne moiety in **176**, **181**, **182** and **183** was reduced to the alkene using Red-Al® and the remaining TIPS-groups were removed using TBAF in THF (scheme 2.28. Thus, the (*6S*), the (*6R*) stereoisomers of RIF-2 (each required a total of 15 steps) and the unbranched (*6R*) congener **188** (a total of 8 steps) were available. Although the linear (*6S*)-congener **185** was detected by LC-MS, isolation of the compound proved challenging and only low yields were achieved. The generally low yields

in the reduction step may be attributed to side reactions such as allene formation.[160] Optimizations using different reducing agents or a different set of conditions are necessary to improve the yield and enable a scale up of the synthesis.

Inspired by earlier reports and based on the assumption that RIF-2 (**4**) may originate from a selective enzymatic oxidation of sulfobacin F **9**, the sulfonolipid was oxidized with SeO_2 under microwave irradiation to an inseparable mixture of (*R*) and (*S*)-isomers of **189** at C-6.[43] As the diastereomeric ratio from the oxidation reaction slightly favors the natural isolate, the theory of a biosynthetic oxidation from sulfobacin F is supported. Although the yields for these transformations remained poor, the primary aim was to obtain the compounds for NMR comparison with the natural isolate.



Scheme 2.28: A) Synthesis of sulfonic acids **184**, **186**, **187** and **188**; B) Riley oxidation of sulfobacin F (**9**).

Thus, the NMR-spectra were compared in $MeOD_4$ and DMSO−d_6 with isolated RIF-2 **4** from *A. machipongonensis* PR1 to deduce the most likely stereochemical assignment at C-6 (figure 2.2 and figure 2.3). Similarly to previous observations, the biggest shift difference is not for the stereocenter itself, but rather in the adjacent positions. As such, the protons at C-3 and C-5 differ visibly in both solvents; whereas the proton at C-6 only shows a shift in DMSO. The C-4 proton shows a slight shift, but for the diastereomeric mixture obtained in the oxidation reaction from sulfobacin F, they are not separated. Interestingly, a higher similarity for the proton at C-3 is found for linear congener **188** than for the branched isomer **186** in $MeOD_4$. In DMSO, the peaks for the proton at C-3 are well-aligned.

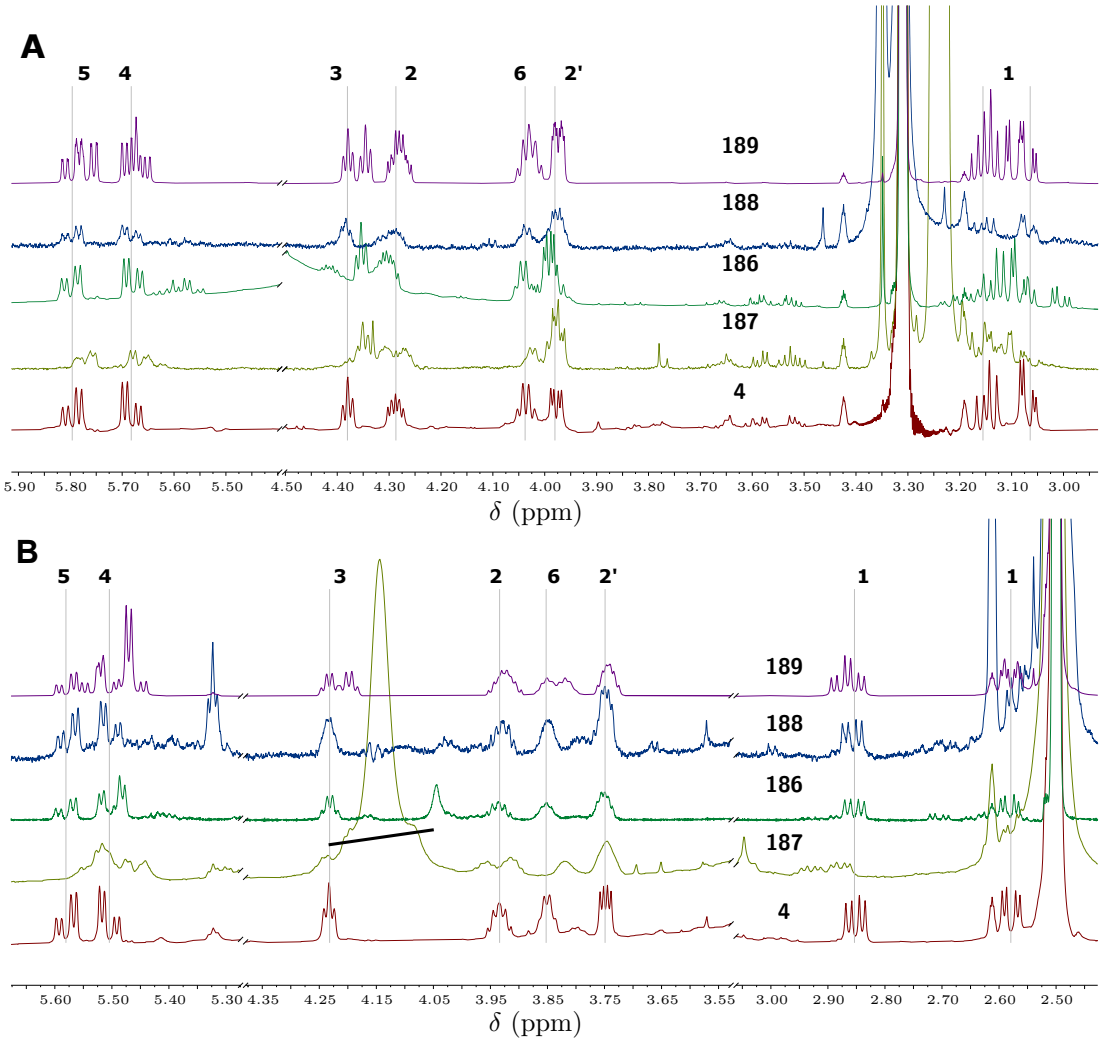


Figure 2.2: ^{1}H-NMR-Comparison of all RIF-congeners; A) in $MeOD_4$; B) in DMSO−d_6.

Comparing the $^{1}H/^{13}C$-HSQC of the isolate with each synthetic deprotected sulfonic acid leads to similar conclusions (figure 2.3). The shifts for the branched isomer (*6R*)-**186** differ the most at C-3 ($MeOD_4$), whereas the spectrum shows very high similarity in DMSO−d_6. For **188** the greatest difference is found for the protons at C-4 and C-5 in $MeOD_4$ and the proton at C-1 in DMSO−d_6, but again the spectra are highly similar. For sulfonic acid **187** more deviation is found in both solvents: the protons at C-3, C-4 and C-5 show shifts in both dimensions and solvents, and C-2' shows a slight shift in the ^{13}C-dimension in $MeOD_4$, whereas the same position has a slight shift in the ^{1}H-dimension in DMSO−d_6. Thus, C-6 is likely to have a (*R*)-configuration, as the (*R*) configured spectra show a better overall match. This finding is in good agreement with the overall structural similarity to 6-OH sphingolipids and ceramides. However, there are shifts in these compounds as well, which remain unexplained and it can only be speculated, that another stereocenter is differently configured than the present compounds. Ultimately, the identity of the synthetic sulfonolipids with RIF-2 needs to be confirmed by their rosette-inducing activity. Studies researching these properties revealed no activity for the synthetic compounds, neither for the total synthesized sulfonolipids **186**, **187** and **188** nor the sulfobacin oxidation-derived compound mixture **189**.[161]

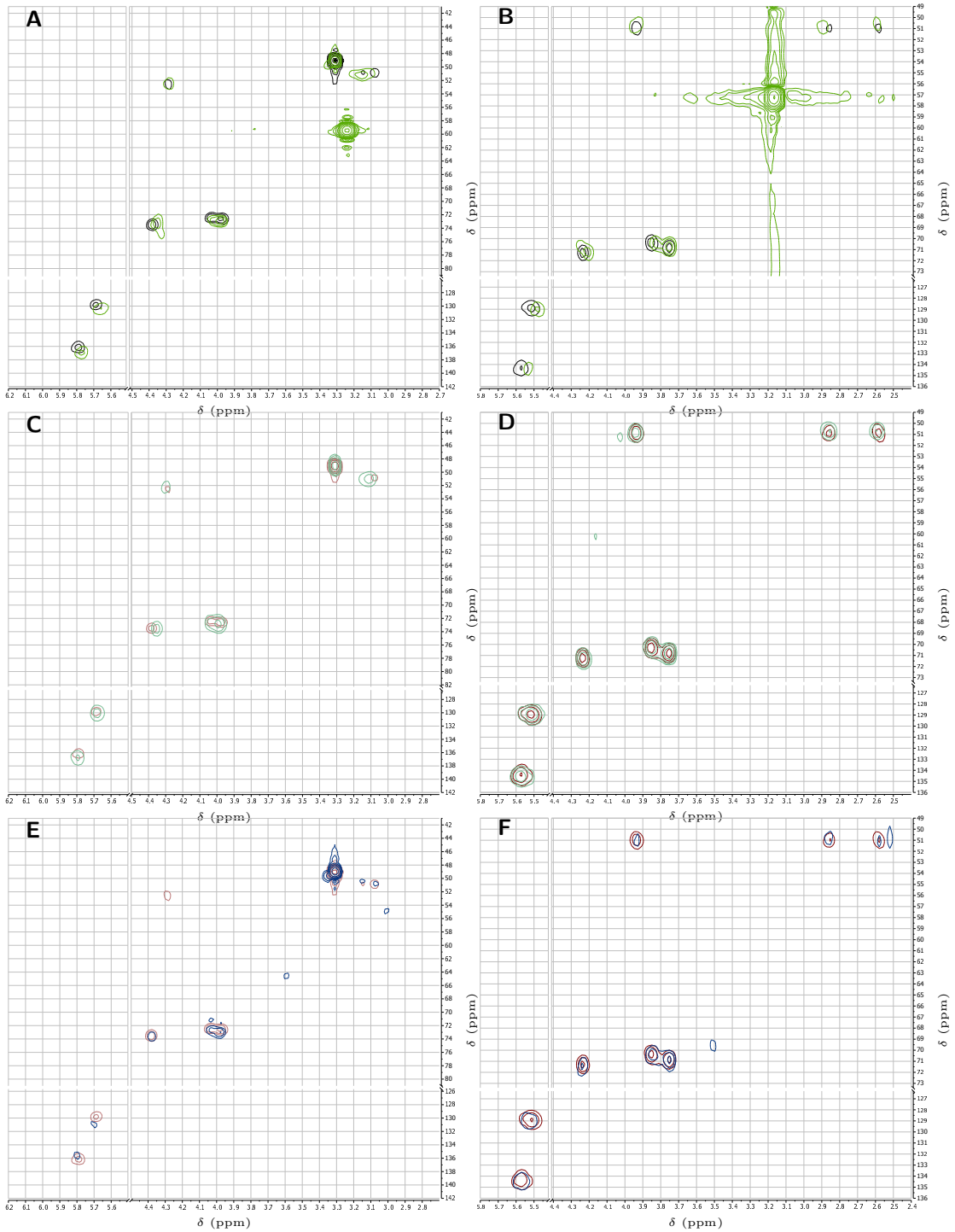


Figure 2.3: $^{1}H/^{13}C$-HSQC comparison of **4** with A) **187** in $MeOD_4$; B) **187** in DMSO−d_6; C) **186** in $MeOD_4$; D) **186** in DMSO−d_6; E) **188** in $MeOD_4$; F) **188** in DMSO−d_6.

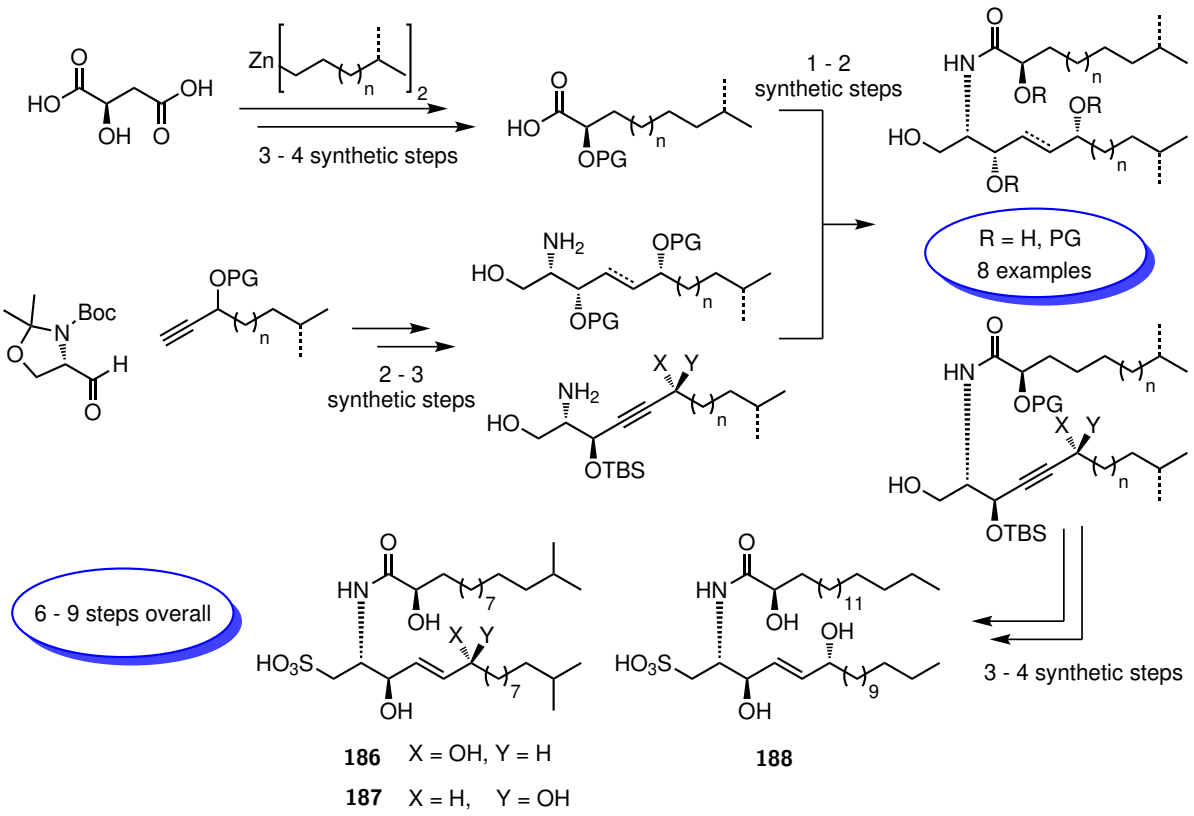
2.6 Conclusion and outlook

In summary, the total synthesis of ceramides and sulfonolipids was accomplished. Using the Garner's aldehyde strategy combined with a hydrozirconation/transmetallation reaction and a three step one pot protection/deprotection sequence, eight unnatural (*3S*)-6-OH ceramides with different chain length and hydroxylation pattern in the acyl part were available. This required four to six synthetic steps in the longest linear sequence from literature known starting material or eight to ten synthetic steps (longest linear sequence) from commercially available starting material. Additionally, one derivative carrying a fluorophore and one derivative carrying a terminal alkyne were synthesized following the same route. This concedes well with literature-known procedures, which require at least four steps from the starting materials to generate the (*3R*)-6-OH ceramides (see scheme 1.2).

On the route towards sulfonolipids, the cysteine route was abandoned due to poor stereoselectivity in the addition step and the failure to deprotect the *N*-Boc-group . While the thioligation route was pursued, thioesters were obtained. However, no ligation to the *N*-acylated product was observed, again, mainly due to the fact that the *N*-Boc-group could not be cleaved. Both strategies may be improved by a different protecting group strategy, these new and more efficient ways of approaching sulfonolipids are worth exploring.

Finally, four (*3R*)-6-OH alkyne ceramides were available via the Garner's aldehyde approach with the same step count as their (*3S*)-congeners using a deprotonation/addition sequence of protected alkynols to aldehyde **11**. From these four protected derivatives, three were converted into the fully deprotected sulfonic acids using a Mitsunobu reaction followed by oxidation in three to four synthetic steps. Additionally, the biomimetic synthesis of a **RIF-2** diastereomeric mixture through an allylic oxidation of **sulfobacin F** was pursued.

To conclude, all obtained sulfonolipids were compared regarding their NMR-spectra and bioactivity with isolated **RIF-2**, and although the NMR spectra show very high similarity for (*2R,2'R,3R,6R*)-configured sulfonolipids **186** and **188** the bioactivity remains illusive. This intriguing result means that further studies need to be performed to determine the absolute configuration, for example the total synthesis of all possible stereoisomers. The synthesis outlined in this thesis provides the required tools.



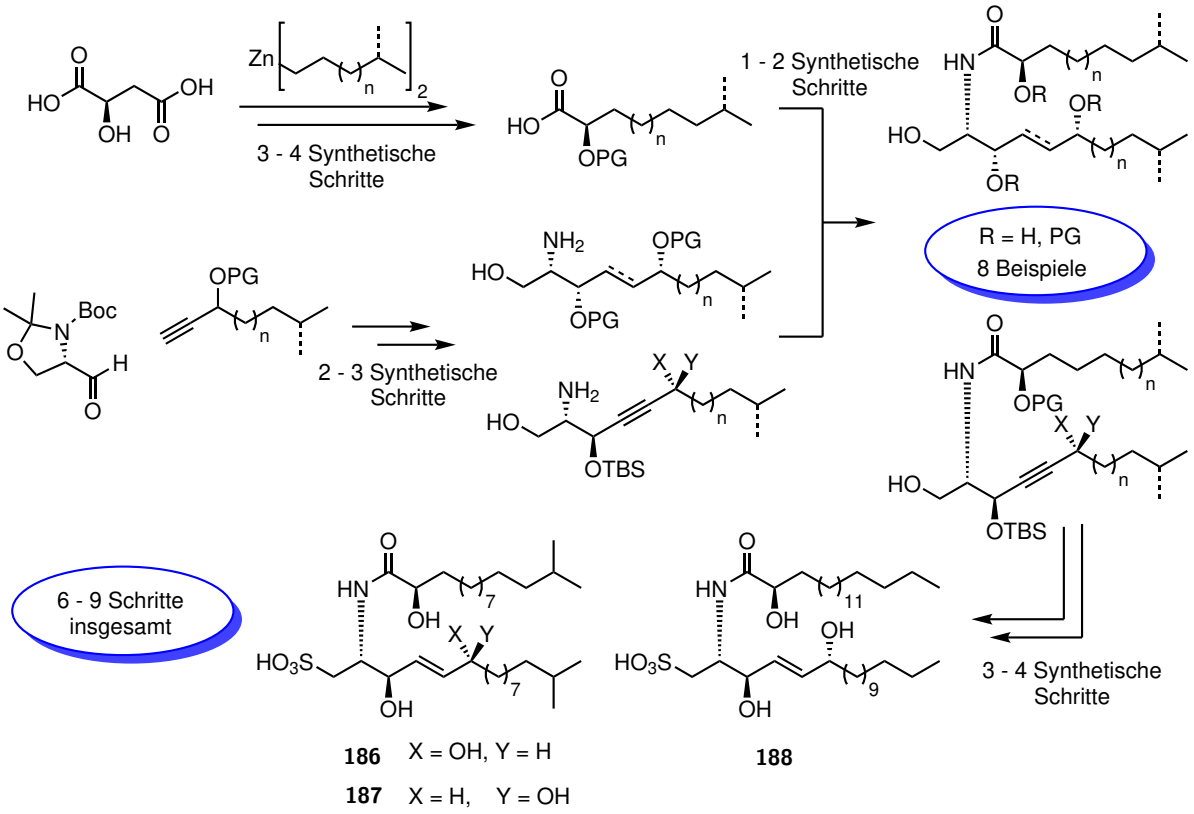
Scheme 2.29: Summary of synthesized molecules including the number of steps needed.

2.7 Zusammenfassung und Ausblick

Zusammenfassend lässt sich sagen, dass die Totalsynthese von Ceramiden und Sulfonolipiden gelungen ist. Unter Verwendung der Garner-Aldehydstrategie in Kombination mit einer Hydrozirkonierungs-/Transmetallierungsreaktion und einer dreistufigen Ein-Topf-Schutz/Entschützungssequenz waren acht unnatürliche (*3S*)-6-OH-Ceramide mit unterschiedlichen Kettenlänge und Hydroxylierungsmustern im Acylteil verfügbar. Dies erforderte vier bis sechs Syntheseschritte (längste lineare Sequenz) aus literaturbekanntem Ausgangsmaterial oder acht bis zehn Syntheseschritte (längste lineare Sequenz) aus kommerziell verfügbarem Ausgangsmaterial. Außerdem wurden ein Derivat mit einem Fluorophor und ein Derivat mit einem terminalen Alkin auf demselben Weg synthetisiert. Dies deckt sich gut mit den in der Literatur bekannten Verfahren, die mindestens vier Schritte aus den Ausgangsmaterialien erfordern, um die (*3R*)-6-OH-Ceramide zu erzeugen (siehe Schema 1.2).

Auf dem Weg zu den Sulfonolipiden wurde die Cystein-Route aufgrund der schlechten Stereoselektivität im Additionsschritt und der nicht durchführbaren Entschützung des *N*-Boc-Gruppe aufgegeben. Des Weiteren wurde die Thioligationsroute weiterverfolgt, wobei Thioester erhalten wurden. Eine Ligation zum *N*-acyliertem Produkt wurde jedoch nicht beobachtet, was hauptsächlich darauf zurückzuführen ist, dass die *N*-Boc-Gruppe nicht abgespalten werden konnte. Beide Strategien könnten durch eine andere Schutzgruppenstrategie verbessert werden; diese neuen und effizienteren Wege der Annäherung an Sulfonolipide sind es wert, erforscht zu werden.

Schließlich waren vier (*3R*)-6-OH-Alkin-Ceramide über den Garner-Aldehyd-Ansatz in der gleichen Anzahl von Schritten wie ihre (*3S*)-Kongenere verfügbar, wobei eine Deprotonierungs-/Additionssequenz von geschützten Alkinolen zum Aldehyd **11** verwendet wurde. Von diesen vier geschützten Derivaten wurden drei durch eine Mitsunobu-Reaktion und anschließende Oxidation in drei bis vier Syntheseschritten in die vollständig entschützten Sulfonsäuren überführt. Darüber hinaus erfolgte die biomimetische



Scheme 2.30: Übersicht über die hergestellten Moleküle mit der Zahl der benötigten synthetischen Schritte.

Synthese eines RIF-2-Diastereomerengemischs durch eine allylische Oxidation von Sulfobacin F.

Anschließend wurden alle erhaltenen Sulfonolipide hinsichtlich ihres NMR-Spektrums und ihrer Bioaktivität mit isoliertem **RIF-2** verglichen, und obwohl die NMR-Spektren für (*2R,2'R,3R,6R*)-konfigurierte Sulfonolipide **186** and **188** eine sehr hohe Ähnlichkeit aufweisen, kinnte nur das natürliche Isolat die Kolonienbildung induzieren. Dieses erstaunliche Ergebnis bedeutet, dass weitere Studien durchgeführt werden müssen, um die absolute Konfiguration von **RIF-2** zu bestimmen, zum Beispiel die Totalsynthese aller möglichen Stereoisomere. Die in dieser Arbeit beschriebene Synthese liefert die dafür nötigen Werkzeuge.

3 Projects related to other natural products

3.1 Synthesis of serine amide derivatives

Despite their vast biological roles, supply of sphingolipids and ceramides remains an issue. Although they play an essential role in maintaining a healthy skin barrier, their supplementation for skin therapeutics remains difficult due to the long reaction sequences. Serine esters on the other hand provide simpler analogs of ceramides and are more easily accessible.[162,163] Apart from their potential therapeutic use, serine amides have been found responsible for slowing down bone degradation in mice.[164]

Following this analogy to the sulfonolipids, cysteic acid derivatives are similarly of great interest, but so far unexplored. Thus, using the previously acquired knowledge, investigations were performed to evaluate synthetic pathways to both product classes.

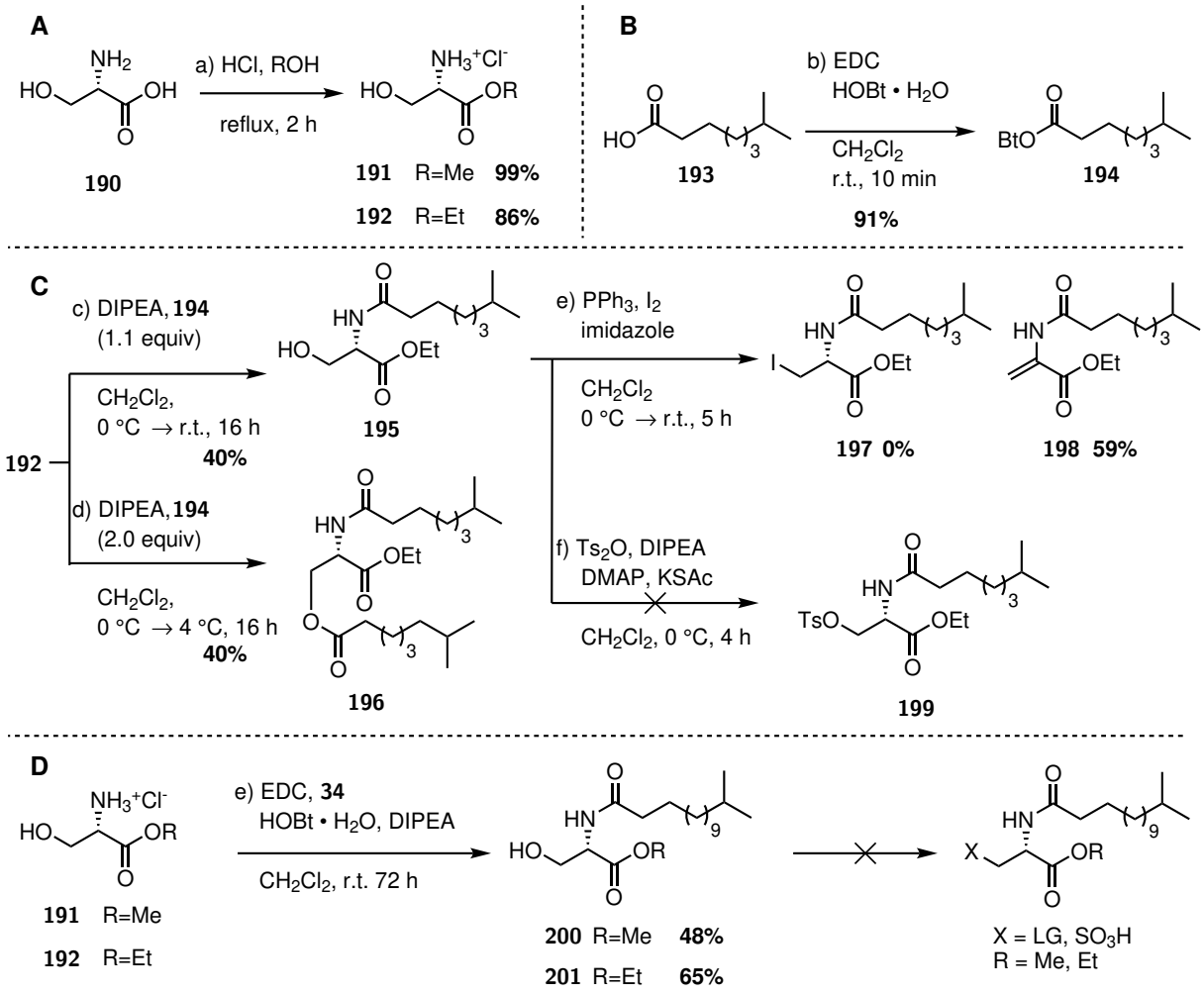
The synthesis started with the assembly of serine amides (scheme 3.1). Serine esters **191** and **192** were synthesized in 86 – 99 % yield from serine by acidic esterification with HCl. Then, ethyl ester **192** was coupled with active ester **194** to furnish amide **195** in 40 % yield. Ester bond formation was observed on top of the desired amide bond formation when two equivalents of HOBt ester **194** with respect to the amine were used in an effort to improve the yield (scheme 3.1C).

Subjecting **195** to iodination reaction conditions only yielded the elimination product **198** (scheme 3.1C). Activation and *in situ* replacement protocols are also known,[165] and KSAc was added to the tosylation reaction mixture; however, neither tosylation nor substitution was observed.

In a different approach, peptide coupling with the *in situ*-generated HOBt ester gave serine amides **200** and **201** in 48 – 65 % yield (scheme 3.1D).

Then ethyl ester **201** was reacted with HSAc under Mitsunobu conditions to thioacetate **SI-24** in 28 % yield, which was then submitted to mild oxidation conditions with H_2O_2 and NH_5CO_3. However no sulfonic acid was formed during the oxidation and different ways to directly introduce the sulfonic acid moiety were investigated. These used the *in situ* substitution of different leaving groups with SO_2 or sulfite salts as nucleophiles. Tosylation as activation method usually resulted in incomplete conversion to a product mixture with peaks in the crude NMR that may belong to elimination products. Further peaks were observed in the alcohol region, which prevented complete structural analysis together with inconsistent integration results and isolation of the products remained elusive. A change to more neutral PPh_3/NBS or Mitsunobu reaction conditions as activating systems resulted in no conversion or product mixtures.

Overall, the synthesis of three serine fatty acid amides has been performed in two steps from natural serine in an overall yield of 34 – 56 %. Converting these into the respective cysteic acid amides proved troublesome and needs further investigations. Alternatively, the use of cysteine as starting molecule may provide the cysteic acid amides after oxidation as well.



Scheme 3.1: Synthesis of serine amides.

3.2 Derivatization of rubterolones

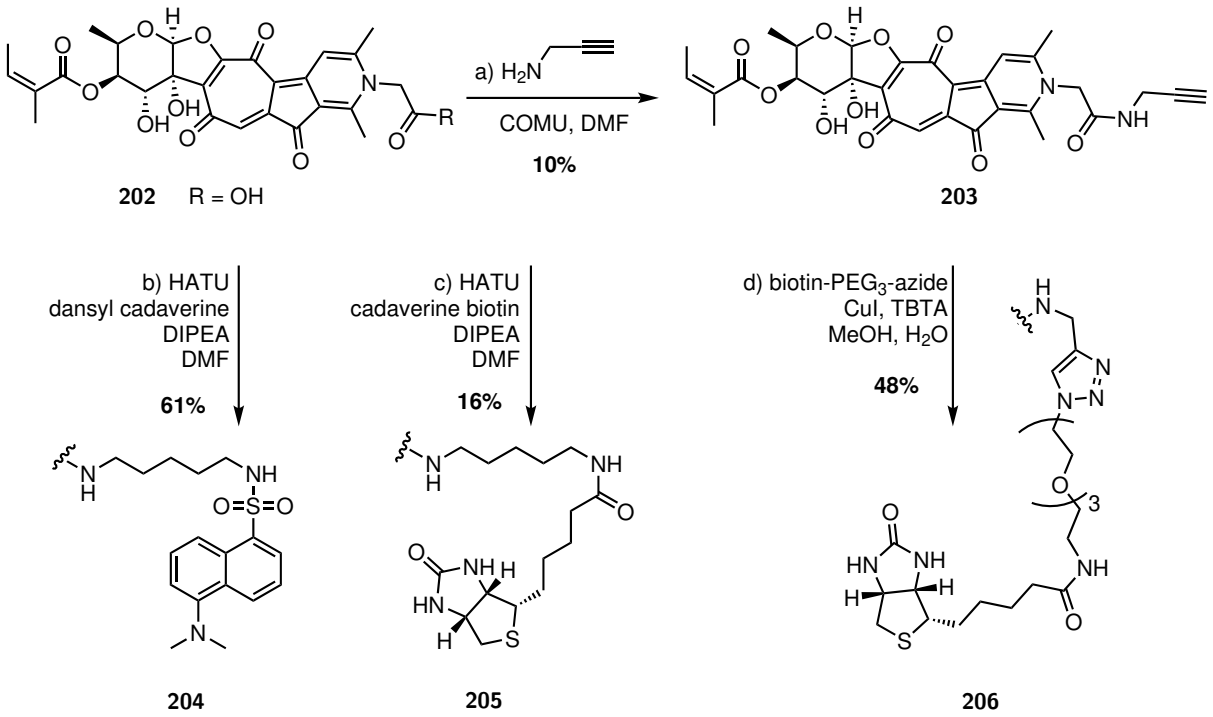
In the chemical ecological context of the fungus-growing termite *Macrotermes natalensis* the bacteria associated with the termite gut of workers have been analyzed for the abundance of natural products.[166] As termite workers are responsible for the construction of the monocultured fungus garden using fecal deposits of predigested plant material, gut bacteria are considered important for garden homeostasis.[167] Thus, *Actinomadura* sp. 5-2 (RB29) was isolated and showed the production of potentially novel active natural products during growth studies and dereplication. Comparative metabolomics, ^{13}C-labeling experiments, genomics and X-ray crystallography revealed the structure of the new tropolone natural products, named rubterolones.

Intriguingly, studying different growth conditions for this bacterium indicated that addition of amino acids enhanced the production of rubterolone derivatives which carry a *N*-substituted pyridine moiety. As such, compound **202** was found when supplementing the medium with glycine. This prompted the investigation to chemically modify the rubterolones for further biological applications. The aim was to introduce tags, which could help identify the biological targets of the rubterolones and thus lead to a better understanding of the processes involved.

Hence, rubterolone D **202** was coupled with propargylic amine using standard peptide coupling conditions with COMU as reagent (scheme 3.2). Despite several free OH-groups, the coupling proceeded smoothly and delivered **203** in 10 % yield, which can be used as a tool in the Cu-catalyzed azide alkyne click-

chemistry (CuAAC) as shown in the reaction with PEG_3-linked biotin azide.[168] This also exemplifies the use of **206** as a tool compound for other modifications.

The peptide coupling with HATU and cadaverine linked fluorescence and biotin tags produced the modified rubterolones **204** and **205**. While the dansyl group, a wide-spread applicable chemical probe used, e.g., in cell membrane studies,[169] helps with the identification in the cell extract, the biotin tag can be used to accumulate the target protein *via* affinity chromatography.[170]



Scheme 3.2: Chemical derivatization of rubterolone D **202**.

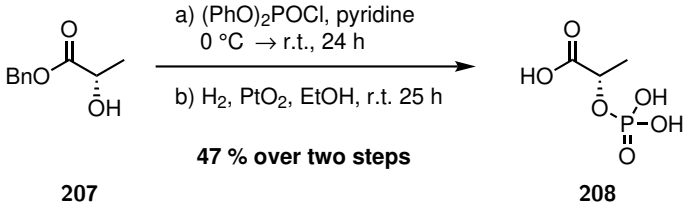
3.3 Synthesis of 2-phospholactate

Cofactors are essential for the catalytic power of many enzymes and thus play a key role in virtually all metabolic pathways. Coenzyme F420 is a specialized redox cofactor with a negative redox potential. It supports biochemical processes like methanogenesis, degradation of xenobiotics and the biosynthesis of antibiotics.[171–173] Although well-studied in methanogenic archaea and actinobacteria, not much is known about F420 in Gram-negative bacteria. Genome sequencing revealed F420 biosynthetic genes in the Gram-negative, endofungal bacterium *Paraburkholderia rhizoxinica*, a symbiont of phytopathogenic fungi.

However, HRMS analysis did not show the expected product mass in the bacteria or the host fungus. When expressing these genes heterologously in *Escherichia coli*, similarly no F420 was found in the HRMS-analysis. To verify the function of the enzyme in the F420 biosynthesis, the precursor 2-phospholactate **208** (2-PL) was required. By adding the putative biosynthetic precursor 2-PL to the purified enzyme, conversion to F420 may be observed. Since 2-PL is not commercially available, a short and efficient synthesis was needed.

In 2001, White *et al.* described the biosynthesis of F420 in methanoarchaea, and therein also a synthetic approach to 2-PL. There, (*S*)-benzyl lactate was reacted with diphenyl phosphoryl chloride in pyridine and in a second step the benzyl and phenyl groups were cleaved with hydrogen using PtO_2.[174] The application of these conditions yielded 2-PL **208** in 47 % yield over two steps.

The use of 2-PL in the enzymatic essay showed no conversion to F420, however additionally oxygenated 3-phosphoglycerol (3-PG) derived cofactors could be isolated. This means, that *Paraburkholderia rhizoxinica* produces a so far unknown cofactor relying on a different phosphoric ester. Ultimately, this may enable the identification of redox-active co-factors in more species.



Scheme 3.3: Synthesis of 2-phospholactate **208**

4 Experimental section

4.1 Methods and materials

NMR measurements were performed on a 300 MHz Bruker AVANCE II, a 500 MHz Bruker AVANCE III and a 600 MHz Bruker AVANCE III spectrometer, equipped with a Bruker Cryoplatform. The chemical shifts are reported in parts per million (ppm) relative to the solvent residual peak of $CDCl_3$ (^{1}H: 7.26 ppm, singlet; ^{13}C: 77.16 ppm, triplett) DMSO-d_6 (^{1}H: 2.50 ppm, quintet; ^{13}C: 39.52 ppm, heptet), D_3COD (^{1}H: 3.31 ppm, quintet; ^{13}C: 49.00 ppm, heptet), C_6D_6 (^{1}H: 7.16 ppm, singlet; ^{13}C: 128.06 ppm, triplett), H_3PO_4 (^{31}P 0.00 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, br. = broad.

UHPLC-ESI-HRMS measurements were carried out on an Accela UPLC system (Thermo Scientific) coupled with an Kinetex Phenyl-Hexyl column (50 x 2.1 mm, particle size 1.7 µm) combined with a Q-Exactive mass spectrometer (Thermo Scientific) equipped with an ESI source.

UHPLC-MS measurements were performed on a Shimadzu LCMS-2020 system equipped with single quadrupole mass spectrometer using a Kinetex C18 column (50 x 2.1 mm, particle size 1.7 µm, pore diameter 10 nm, Phenomenex) and a Kinetex Phenyl-Hexyl column (50 x 2.1 mm, particle size 1.7 µm, pore diameter 10 nm, Phenomenex). Column oven was set to 40 °C; scan range of MS was set to m/z 150 to 2,000 with a scan speed of 10.000 u/s and event time of 0.25 s under positive and negative mode. DL temperature was set to 250 °C with an interface temperature of 350 °C and a heat block of 400 °C. The nebulizing gas flow was set to 1.5 L/min and dry gas flow to 15 L/min.

Semi-preparative HPLC was performed on a Shimadzu HPLC system using a Gemini C18(2) 250 x 10 mm column (particle size 5 µm, pore diameter 10 nm, Phenomenex) and a Luna Phenyl-Hexyl 250 x 10 mm column (particle size 5 µm, pore diameter 10 nm, Phenomenex).

Preparative HPLC was performed on a Shimadzu HPLC system using a Luna Phenyl-Hexyl 250 x 21.2 mm column (particle size 5 µm, pore diameter 10 nm, Phenomenex).

Chiral analytical HPLC was performed on a Knauer Smartline HPLC system using a Phenomenex Lux Cellulose-1 column (250 x 4.6 mm, particle size 5 µm, pore diameter 10 nm).

Flash chromatography was performed on a Biotage Isolera™ Prime. Pre-coated silica gel 60 F254 plates (Merck) were used for TLC with detection of compounds *via* UV, $KMnO_4$, phosphomolybdic acid/$CeSO_4$ or anisaldehyde stains.

IR spectra were recorded on an FT/IR-4100 ATR spectrometer (JASCO).

Optical rotations were recorded in the respective solvent on a P-1020 polarimeter (JASCO).

Methanol (VWR, Germany), water (Millipore, Germany) for analytical and preparative HPLC, formic acid (Carl Roth, Germany) and acetonitrile (VWR as LC-MS grade) were used without further purification. Ti(O*i*−Pr)$_4$ was dried under high vacuum and dissolved in dry toluene prior to use. DCC was purchased from Fluorochem and melted under vacuum prior to use. All other reagents and solvents for

synthesis were purchased from Acros Organics, Alfa Aesar, Carbolution Chemicals, Carl Roth, Fluorochem, Sigma Aldrich, TCI, Th. Geyer and VWR and used without further purification. All reactions were performed in flame-dried glassware under argon atmosphere, unless otherwise stated.

4.2 General Procedures

General Procedure 1 (GP 1) for Cu-mediated Grignard reaction

A solution of *i*-butyl magnesium bromide (2 M solution in Et_2O, 2.50 equiv) was added dropwise to a solution of the respective ω-bromo-alcohol (1.00 equiv) in THF (5 mL/mmol) at −78 °C. The reaction was stirred for 15 min and treated with a solution of Li_2CuCl_4 (0.1 M in THF, 0.05 equiv). After stirring at −78 °C for 1 h, the mixture was allowed to warm to r.t. overnight. The dark blue mixture was cooled to 0 °C, *i*-PrOH and NH_4Cl solution were added and the aqueous phase extracted with TBME (3x). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the alcohol, which was used without further purification.

General Procedure 2 (GP 2) for oxidation of primary alcohols to the carboxylic acids

Solid $KMnO_4$ (3.00 equiv) was added to a solution of the respective alcohol (1.00 equiv) in *tert*-BuOH (2.3 mL/mmol). Brown precipitate formed from the initial purple suspension upon addition of an aqueous solution of NaOH (2 M, 4.50 equiv). After stirring at r.t. for 16 h, the mixture was cooled to 0 °C and sat. $Na_2S_2O_5$ solution was added carefully. The brown precipitate was slowly filtered into conc. aq. HCl at 0 °C over a pad of Celite and thoroughly washed with water and TBME. The filtrate was extracted with TBME (3x), the combined organic phase washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude carboxylic acid, which was used without further purification.

General Procedure 3 (GP 3) for Davis oxidation

A solution of the respective oxazolidinone (1.00 equiv) in dry THF (3 mL/mmol) was added to a solution of KHMDS (1.50 equiv, 0.7 M in toluene) in THF (3 mL/mmol) at −78 °C and the slurry stirred for 30 min. A pre-cooled (−78 °C) solution of Davis' oxaziridine **SI-3** (2.50 equiv) in dry THF (10 mL/mmol) was added and the mixture stirred at −78 °C for 2 h. The reaction was stopped by addition of camphorsulfonic acid (4.00 equiv) in THF (1 mL/mmol acid) at −78 °C followed by addition of saturated NH_4Cl solution. After warming to r.t., the aqueous phase was extracted with TBME (3x), the combined organic phase was washed with Na_2CO_3 solution, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 4 (GP4) for removal of the auxiliary

A solution of LiOH (3.00 equiv) and H_2O_2 (6.00 equiv) in H_2O (1.00 mL/mmol was added to a solution of the respective oxazolidinone in BHT-stabilized THF (6.00 mL/mmol) at 0 °C. The reaction was stirred at 0 °C for 16 h and stopped by addition of sat. NaS_2O_3 solution. EtOAc was added, the mixture centrifuged, the organic phase collected and the process repeated two more times. After acidifying of the aqueous phase with 1 M HCl, the mixture was extracted with EtOAc (3x), the combined acidic organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 5 (GP 5) for the preparation of diorganozinc reagents

Magnesium-turnings (2.40 equiv) were covered in THF under argon atmosphere and 1,2-dibromoethane (0.1 equiv) was added dropwise, which resulted in gas formation. Upon ceasing of the gas formation, a spatula tip of I_2 was added, which turned the colorless suspension brown. Then, 10 % of the total volume of the respective alkyl bromide (2.00 equiv) in THF (1 mL/mmol) was added at once, which resulted in disappearance of the color and boiling of the solvent. Dropwise addition was maintained to continue refluxing. The dark gray suspension was stirred without further heating until titration vs. I_2 in saturated LiCl solution (in THF) gave a satisfactory concentration of the Grignard reagent. Meanwhile, $ZnCl_2$ was dried in high-vacuum at 190 °C for 3 h and then dissolved in THF (1 mL/mmol). The Grignard solution was transferred to the $ZnCl_2$ solution, resulting in intermediary precipitation and heat development. The mixture was stirred for 15 min, until the suspension dissolved, and then used freshly prepared for the next step.

General Procedure 6 (GP 6) for the decarboxylative cross coupling

N-Methylmorpholine (2.20 equiv) was added to a yellow solution of the respective carboxylic acid (1.00 equiv) and CITU (1.10 equiv) in DMF (10 mL/mmol acid), which turned the color to orange, and the mixture stirred at r.t. for 15 min. A freshly prepared light green solution of $NiCl_2 \cdot$ glyme (0.2 equiv) and 4,4′-di-*tert*-butyl-2,2′-dipyridine (0.40 equiv) in DMF (50 mL/mmol $NiCl_2$) was added dropwise at r.t. while cooling in a water bath, followed by addition of the freshly prepared organo zinc-reagent (2.00 equiv). The dark green suspension was stirred at r.t. for 16 h and cooled to 0 °C. Cyclohexane and 1 M HCl (or saturated NH_4Cl solution for acid sensitive substrates) were added and the aqueous phase extracted with cyclohexane. The combined organic phase was washed with H_2O, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 7 (GP 7) for olefin cross-metathesis

The respective commercially available alkene (20 equiv) and Hoveyda-Grubbs II-catalyst (0.04 equiv) were added to a solution of the respective terminal alkene (1.00 equiv) in CH_2Cl_2 (20 mL/mmol) and the suspension was refluxed for 3 h. The volatiles were removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 8 (GP 8) for hydrogenation reaction

Pd/C (wetted with 50 % H_2O, 0.1 equiv) was added to a solution of the respective alkene (1.00 equiv) in EtOAc (10 mL/mmol) and H_2-gas was bubbled through the suspension at r.t. for 10 min. The slurry was stirred under H_2-atmosphere until all starting material was consumed as evidenced *via* TLC, usually 1 h. The suspension was filtered over a pad of Celite and the volatiles removed *in vacuo* to yield the crude product, which was used without further purification.

General Procedure 9 (GP 9) for acidic hydrolysis of the ester-acetonide

1 M aq. HCl (12.0 equiv) was added to a solution of the respective acetonide (1.00 equiv) in THF (13 mL/mmol) and the two-phase mixture was stirred in a sealed tube under microwave irradiation at 110 °C for 5 min. After cooling to r.t., brine was added to the mixture and the aqueous phase extracted with EtOAc (3x). The combined organic phase was dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude product, which was used in the next step without further purification.

General Procedure 10 (GP 10) for thionylation reaction

Lawesson's reagent (0.55 equiv) was added to a solution of the respective carbonyl compound (1.00 equiv) in toluene/$CHCl_3$ (10/1, 10 mL/mmol) and the smelly suspension was stirred in a sealed tube under microwave irradiation at 120 °C for 7.5 min. After cooling to r.t., the volatiles were removed *in vacuo* to yield the crude product, which was directly used without further purification.

General Procedure 11 (GP 11) for acid chloride formation and Friedel-Crafts-type acylation

The respective carboxylic acid (1.00 equiv) was dissolved in $SOCl_2$ (7.00 equiv) and stirred at r.t. for 16 h. The volatiles were removed *in vacuo* yielding the crude acid chloride, which was used without further purification.

A solution of the respective acid chloride (1.00 equiv) in CH_2Cl_2 (0.5 mL/mmol) was added to a suspension of $AlCl_3$ (1.50 equiv) in CH_2Cl_2 (1 mL/mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min, after which bis(trimethylsilyl)acetylene (1.10 equiv) was added in several portions. The reaction was allowed to warm to r.t., stirred for 3 h, poured onto ice and extracted with CH_2Cl_2 (3x). The combined organic phase was washed carefully with sat. $NaHCO_3$ solution due to strong gas formation and the aqueous phase extracted again with CH_2Cl_2. The combined organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash-chromatography.

General Procedure 12 (GP 12) for Noyori-type reduction

RuCl[(*R*,*R*)-TsDPEN](mesitylene) (2.5 mol %) and a cooled solution of Et_3N (6.00 equiv) and formic acid (5.00 equiv) in *i*-PrOH (2.0 mL/mmol) were added to a solution of the respective TMS-alkynone (1.00 equiv) in *i*-PrOH (2.0 mL/mmol). The dark brown solution was stirred at r.t. for 6 h until complete consumption of the starting material on TLC was observed. The reaction was quenched by the addition of NH_4Cl solution and the aqueous phase extracted with TBME (3x). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General procedure 13 (GP 13) for TMS-deprotection

A solution of the respective alkynol (1.00 equiv) in CH_2Cl_2 (1.0 mL/mmol) was added to a solution of KOH (4.00 equiv) in MeOH/H_2O (1/1, 5.0 mL/mmol) and stirred at r.t. for 16 h. The mixture was acidified with 1 M HCl and extracted with TBME (3x). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield the crude, which was used in the next step without further purification.

General Procedure 14 (GP 14) for silylprotection

TBSCl (1.40 equiv) was added in several portions to a solution of the respective alkynol (1.00 equiv), DIPEA (1.70 equiv) and 4-DMAP (0.10 equiv) in DMF (1.0 mL/mmol) and the mixture was stirred at r.t. for 20 h. The reaction was quenched by addition of 10 % aq. citric acid solution and extracted with cyclohexane (3x). The combined organic phase was washed with sat. Na_2CO_3 solution, brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield the crude product, which was used in the next step without further purification.

General Procedure 15 (GP 15) for silylprotection with silyltriflates

The specified silyl triflate (1.10 equiv) was slowly added to a solution of the respective alcohol (1.00 equiv) and 2,6-lutidine (3.50 equiv) in CH_2Cl_2 (3.0 mL/mmol) at 0 °C and the mixture stirred for 1 h. If no conversion was observed, the reaction was stirred at r.t. for 2 – 16 h. The reaction was quenched by addition of Na_2CO_3 solution, the aqueous phase extracted with CH_2Cl_2 and the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 16 (GP 16) for a hydrometalation reaction

the respective metal organyl (1.10 equiv) was added to a solution of alkyne **79** (1.05 equiv) in the respective solvent (1.0 mL/mmol) at the temperature indicated and stirred for the given time.

If Et_2Zn was used, the mixture was cooled to −40 °C and treated with Et_2Zn (0.9 M in hexanes, 1.21 equiv), stirred for 15 min, followed by addition of Garner's aldehyde **11** (1.00 equiv) at −40 °C. The reaction was stirred for the indicated time and worked up by adding sat. NH_4Cl solution or sat. Na/K-tartrate solution. The aqueous phase was extracted with TBME, washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo*.

The crude product was dissolved in MeOH/THF (3/1, 1 mL/mmol) and treated with $NaBH_4$ (3 mg, 81.0 µmol, 0.29 equiv) at 0 °C. The mixture was stirred at r.t. for 30 min, AcOH (5 µL, 87 µmol) was added and the volatiles were removed *in vacuo*. The residue was filtered over a silica pad and purified by flash chromatography.

General Procedure 17 (GP 17) for a hydrozirconation reaction

The respective alkyne (1.10 equiv) was added dropwise to a suspension of Schwartz's reagent (1.10 equiv) in CH_2Cl_2 (1.0 mL/mmol) at 0 °C and the initially colorless suspension was stirred at r.t. to turn into a yellowish solution. After 3 h the mixture was cooled to the temperature indicated and Et_2Zn (1.20 equiv, 0.9 M solution in hexanes) and the indicated additives were added dropwise. After stirring for 15 min, Garner's aldehyde **11** (1.00 equiv) in CH_2Cl_2 (1.0 mL/mmol) was added at the indicated temperature. The reaction was stirred for the specified time and quenched by addition of sat. Na/K-tartrate solution. The mixture was filtered through a pad of Celite and thoroughly washed with H_2O and EtOAc. The filtrate was extracted with EtOAc (3x), the combined organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 18 (GP 18) for alkyne additions to Garner's aldehyde 11

n-BuLi (1.50 equiv) was added dropwise to a solution of the respective alkyne (1.20 equiv) in THF (2 mL/mmol) at −78 °C and the mixture was stirred for 30 min. As pecified in each procedure, DMPU (9.00 equiv) or HMPA (4.00 equiv) was added, followed by a solution of Garner's aldehyde **11** (1.00 equiv) in THF (2 mL/mmol). The reaction was stirred at −78 °C for 30 min, then allowed to warm to r.t. over 16 h. NH_4Cl-solution was added, the mixture extracted with TBME and the combined organic phase was washed with H_2O, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 19 (GP 19) for Boc-deprotection

TBSOTf (1.10 equiv) was slowly added to a solution of the respective oxazolidine (1.00 equiv) and 2,6-lutidine (3.50 equiv) in CH_2Cl_2 (3.0 mL/mmol) at 0 °C and the mixture stirred for 30 min. After consumption of the starting material, TMSOTf (2.00 equiv) was added dropwise and the mixture was stirred at 0 °C for further 60 min. The reaction was quenched by addition of Na_2CO_3 solution, the aqueous phase extracted with CH_2Cl_2 and the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by reverse-phase flash chromatography.

General procedure 20 (GP 20) for selective acetonide deprotection.

PPTS (0.10 equiv) was added to a solution of the respective acetonide (1.00 equiv) in MeOH (20 mL/mmol) and the mixture was stirred at 60 °C for 1 h. After cooling to r.t., Na_2CO_3-solution was added, the aqueous phase extracted with TBME and the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 21 (GP 21) for amide coupling using HBTU

The respective carboxylic acid (1.10 equiv) and HBTU (1.20 equiv) were dissolved in DMF (20 mL/mmol) at 0 °C and stirred for 5 min. A solution of the corresponding amine (1.00 equiv) and DIPEA (2.50 equiv) in DMF (20 mL/mmol) was added and the mixture was stirred at r.t. until complete consumption of the amine was detected (monitored by TLC, usually 2 h). The reaction was quenched by addition of sat. Na_2CO_3 solution, the aqueous phase extracted with EtOAc (3x) and the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 22 (GP 22) for amide coupling using DCC

DCC (1.20 equiv) was melted under vacuum, dissolved in CH_2Cl_2 (1 mL/mmol), the respective carboxylic acid (1.10 equiv) was added and the mixture stirred at 0 °C and for 15 min. A solution of the corresponding amine (1.00 equiv) and DIPEA (2.50 equiv) in CH_2Cl_2 (1.1 mL/mmol) was added and the reaction stirred at r.t. for 3 h. Sat. Na_2CO_3 solution was added, the suspension filtered over a pad of Celite and the filtrate extracted with EtOAc (3x). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 23 (GP 23) for silyl deprotection using TBAF

TBAF (2.50 equiv, 1 M solution in THF) was added to a solution of the respective silylether (1.00 equiv) in THF (10 mL/mmol) and the solution stirred at r.t. until no starting material was observed on TLC. The mixture was diluted with MeOH, the volatiles were removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 24 (GP 24) for silyl deprotection using HF

Pyridine (10.0 equiv) and HF·pyridine complex (40.0 equiv) were added to a solution of the corresponding silylether (1.00 equiv) in THF (20 mL/mmol) at 0 °C. The mixture was stirred at r.t. for 16 h, sat. Na_2CO_3 solution was added and the aqueous phase extracted with EtOAc. The combined organic phase

was washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by preparative RP-TLC.

General Procedure 25 (GP 25) for Mitsunobu reaction

DIAD (1.90 equiv) was added to a solution of PPh_3 (2.00 equiv) in THF (5 mL/mmol) at 0 °C and the solution stirred at 0 °C for 30 min, during which a precipitate forms. A mixture of the respective alcohol (1.00 equiv) and thiocarboxylic acid (4.00 equiv) in CH_2Cl_2 (10 mL/mmol of the corresponding alcohol) was added to this suspension and the resulting clear solution was stirred at r.t. until complete consumption of the alcohol was observed by TLC (few hours to overnight). CH_2Cl_2 and sat. $NaHCO_3$ solution were added, the aqueous phase extracted with CH_2Cl_2 and the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 26 (GP 26) for oxidation reaction to sulfonic acids

A solution of NaSMe (2.00 equiv) in MeOH (2.00 mL/mmol NaSMe) was added to a solution of the respective thioacetate (1.00 equiv) in CH_2Cl_2 (50 mL/mmol) at 0 °C. The mixture was stirred for 5 min, then *m*-CPBA (10.0 equiv) in CH_2Cl_2 was added at 0 °C, the reaction stirred for 5 min and Me_2S (25.0 equiv) was added at 0 °C. The reaction was warmed to r.t., the volatiles removed *in vacuo* and the crude product purified by flash chromatography.

General Procedure 27 (GP 27) for the reduction reaction to (*E*)-doublebonds

A solution of Red-Al® (25.0 equiv) in toluene (60 %) was added to a solution of the respective alkyne (1.00 equiv) in THF (50 mL/mmol) at 0 °C. The reaction progress was monitored by LC-MS. In 2 h intervals additional Red-Al® (25.0 equiv) was added at 0 °C. After complete conversion, L-(+)-tartaric acid (100 equiv) in MeOH (0.5 M) was added slowly. A few drops of NH_4OH (50 % in H_2O) were added and the suspension stirred at r.t. for 2 h. The mixture was centrifuged (3000 g, 4 °C for 40 min), the supernatant transferred into a vial, the pellet suspended in MeOH and the mixture centrifuged again (3000 g, 4 °C for 40 min). The supernatants were combined, the volatiles removed *in vacuo* and the remains pre-purified *via* SPE-extraction (equilibrate: 60 % MeOH in H_2O + 0.1 % NH_4OH; elute: 100 % MeOH + 0.1 % NH_4OH). The 100 % MeOH-fractions were combined, the volatiles removed *in vacuo* and the crude product purified *via* HPLC.

Determination of enantiomeric excess of the Noyori reduction

A sample of the respective alkynol (6.00 mg, 28.5 mmol) was converted into its 4-bromobenzoyl derivative. Therefore the alcohol was stirred with excess 4-bromobenzoyl chloride in pyridine at r.t. for 2 h, quenched with aqueous NaOH (1 M), extracted with cyclohexane and the volatiles were removed *in vacuo*. The crude product was subjected to chiral HPLC using an isocratic gradient of A/B 80/20 (A = nHex; B= nHex/TBME 9/1).

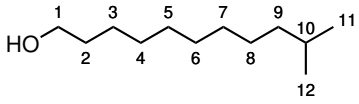
Table 4.1: Determination of the enantiomeric excess of the Noyori reduction.

#	$t_R = 8.6$ min (S) Area	%	$t_R = 11.6$ min (R) Area	%	*ee*
74	1072948	50 %	1065436	50 %	0.35 %
78	26905222	99.1	235238	0.86	96 %
80	101024	0.36	28219387	99.6	98 %

4.3 Synthesis of α-OH fatty acids

10-Methylundecanol (31)

exp: 1
DL488



Magnesium turnings (15.3 g, 627 mmol) were activated using I_2, *i*-propyl bromide (36.8 mL, 392 mmol) in THF (500 mL) was added until the Mg turnings were covered and an exothermic reaction could be monitored. The remaining solution of the bromide was added in such a way that a slight reflux was sustained. Upon complete addition, the reaction mixture was refluxed for 5 d until titration against I_2 in LiCl solution (0.5 M in THF) confirmed the concentration of of the Grignard reagent of 0.8 M. The reaction mixture was cooled to r.t and additional THF (250 mL) was added. The suspension was cooled to −78 °C, 8-bromononanol (35.0 g, 157 mmol) in THF (250 mL) was added dropwise and the mixture stirred at −78 °C for 15 min. Li_2CuCl_4 (16 mL, 0.1 M solution in THF, 16.0 mmol) was added and the reaction was stirred at −78 °C for 1 h followed by warming to r.t. overnight. Next, the reaction mixture was cooled to 0 °C and *i*-PrOH, NH_4Cl solution and 5 M aq. HCl were added carefully, which resulted in a color change from blue to yellow. After complete consumption of the remaining magnesium turnings the solvent was evaporated until 300 mL remained. The residue was extracted with TBME (3x), and the combined organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and filtered over a pad of silica to yield alcohol **31** as a brownish oil (30.0 g, quant.), which was used in the following step without further purification.

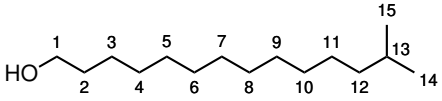
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.64 (t, J = 6.6 Hz, 2 H, 1-H), 1.70 – 1.37 (m, 3 H, 2-H to 10-H), 1.39 – 1.16 (m, 14 H, 3-H to 8-H), 1.23 – 1.04 (m, 2 H, 9-H), 0.86 (d, J = 6.6 Hz, 6 H, 11-H, 12-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 63.3 (t, C-1), 39.2 (t, C-2), 33.0, 30.1, 29.8, 29.6 (4t, C-3 to C-9), 28.1 (d. C-10), 27.6, 25.9 (2t, C-3 to C-9), 22.8 (q, C-11, C-12) ppm.

The analytical data is consistent with literature reports.[76]

13-Methyltetradecanol (32)

exp: 2
DL081



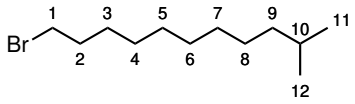
According to GP 1, the reaction of 11-bromoundecanol (2.50 g, 9.95 mmol) with *i*-butylmagnesium bromide (12.4 mL, 24.9 mmol) and Li_2CuCl_4 (10.0 mL, 995 µmol) yielded **32** as a colorless wax (2.34 g, quant.).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.58 (t, J = 6.7 Hz, 2 H, 1-H), 1.61 – 1.45 (m, 3 H, 2-H to 13-H), 1.36 – 1.20 (m, 19 H, 3-H to 12-H), 1.16 – 1.08 (m, 2 H, 12-H), 0.84 (d, J = 6.7 Hz, 6 H, 14-H, 15-H) ppm.

The analytical data is consistent with literature reports.[55]

1-Bromo-10-methylundecane (33)

exp: 3
DL475

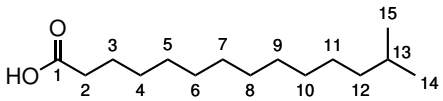


Br_2 (1.80 mL, 34.0 mmol) was added dropwise to a solution of PPh_3 (9.10 g, 34.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C. A colorless precipitate formed and upon complete addition, the suspension turned orange. Alcohol **31** (5.90 g, 31.7 mmol) in CH_2Cl_2 (13.0 mL) was added to this mixture, which dissolved the precipitate. Pyridine (2.81 mL, 34.8 mmol) was added, the reaction stirred at r.t. for 1 h, after which $Na_2S_2O_3$ solution was added slowly at 0 °C. The aqueous phase was extracted with cyclohexane, the combined organic phase washed with 10 % citric acid, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 100/1 → 50/1, eluting at 50/1) to yield **33** as a yellow liquid (7.43 g, 94 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.41 (t, J = 6.9 Hz, 2 H, 1-H), 1.85 (dt, J = 14.4, 6.9 Hz, 2 H, 2-H), 1.58 – 1.47 (m, 1 H, 10-H), 1.42 (ddt, J = 12.5, 10.5, 6.7 Hz, 2 H, 3-H to 8-H), 1.35 – 1.20 (m, 11 H, 3-H to 8-H), 1.20 – 1.07 (m, 2 H, 9-H), 0.86 (d, J = 6.6 Hz, 6 H, 11-H, 12-H) ppm.

13-Methyltetradecanoic acid (34)

exp: 4
DL080



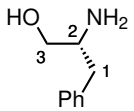
According to GP 2, the reaction of 13-methyltetradecanol (500 mg, 2.19 mmol) with $KMnO_4$ (3.32 g, 21.0 mmol) and NaOH (1.26 g, 31.5 mmol) yielded **34** as a colorless wax (498 mg, 94 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.34 (t, J = 7.5 Hz, 2 H, 2-H), 1.63 (p, J = 7.5 Hz, 2 H, 3-H), 1.51 (hept, J = 6.6 Hz, 1 H, 13-H), 1.40 – 1.22 (m, 16 H, 4-H to 11-H), 1.21 – 1.11 (m, 2 H, 12-H), 0.86 (d, J = 6.6 Hz, 6 H, 14-H), 15-H ppm.

The analytical data is consistent with literature reports.[55]

(*R*)-2-Amino-3-phenylpropan-1-ol (SI-1)

exp: 5
DL319



$BF_3{\cdot}OEt_2$ (22.4 mL, 181 mmol) was added dropwise to a suspension (*R*)-phenylalanine (30.0 g, 181 mmol) in THF (90 mL) at r.t. and the mixture was refluxed for 2 h, during which it became a clear solution. $BH_3{\cdot}Me_2S$ (20.8 mL, 209 mmol) was added over 60 min while sustaining the reflux and continuous gas formation could be monitored. After further 6 h of refluxing the now brownish solution was cooled to

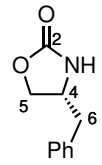
r.t. and THF/H_2O-mixture (1/1, 25 mL) was added slowly, resulting in a precipitate, which dissolved upon further addition. Aqueous NaOH solution (5 M, 150 mL) was added and the two-phase mixture refluxed for 16 h, followed by removal of the volatiles *in vacuo* and extraction of the aqueous phase with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to afford the crude product, which was recrystallized from EtOAc (100 mL) to yield **SI-1** as colorless needles (14.3 g, 52 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.37 – 7.28 (m, 2 H, Ph-H), 7.27 – 7.14 (m, 3 H, Ph-H), 3.63 (dd, J = 10.7, 4.0 Hz, 1 H, 3-H), 3.39 (dd, J = 10.8, 7.2 Hz, 1 H, 3-H), 3.12 (dp, J = 8.7, 4.5 Hz, 1 H, 2-H), 2.79 (dd, J = 13.2, 5.3 Hz, 1 H, 1-H), 2.52 (dd, J = 13.2, 8.6 Hz, 1 H, 1-H), 2.03 (br. s, 1 H, O-H, N-H) ppm.

The analytical data is consistent with literature reports.[78]

(*R*)-4-Benzyloxazolidin-2-one (36)

exp: 6
DL322



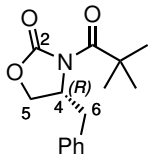
(*R*)-2-Amino-3-phenylpropan-1-ol **SI-1** (14.2 g, 93.9 mmol) and K_2CO_3 (1.30 g, 9.39 mmol) were suspended in diethyl carbonate (22.6 mL, 187 mmol) and the mixture stirred at 135 °C using distillation equipment. Upon dropping of the head temperature below 60 °C (2 h), the reaction was cooled to r.t. and the remaining solid taken up in CH_2Cl_2, washed with H_2O, dried over $MgSO_4$ and filtered. The volatiles were removed *in vacuo* and the crude was recrystallized from hot cyclohexane/EtOAc (2/1) with hot filtration to yield **36** as colorless plates (12.5 g, 75 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40 – 7.23 (m, 3 H, Ph-H), 7.21 – 7.13 (m, 2 H, Ph-H), 4.44 (t, J = 8.1 Hz, 1 H, 4-H), 4.18 – 4.02 (m, 2 H, 5-H), 2.88 (d, J = 6.7 Hz, 2 H, 6-H) ppm.

The analytical data is consistent with literature reports.[78]

(*R*)-4-Benzyl-3-pivaloyloxazolidin-2-one (39)

exp: 7
DL324



39, a side product in the synthesis of **40**, was isolated as a colorless solid (112 mg, 38 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.38 – 7.19 (m, 7 H, Ph-H), 4.70 (ddt, J = 9.5, 7.4, 3.2 Hz, 1 H, 4-H), 4.28 – 3.96 (m, 2 H, 5-H), 3.23 (dd, J = 13.2, 3.3 Hz, 1 H, 6-H), 2.77 (dd, J = 13.2, 9.6 Hz, 1 H, 6-H), 1.40 (s, 9 H, $COC(C\underline{H_3})_3$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 178.7 (s, $\underline{C}OC(CH_3)_3$), 152.5 (s, C-2), 135.7 (s, C-Ph), 129.6, 129.0, 127.4 (3d, C-Ph), 66.3 (t, C-5), 57.5 (d, C-4), 41.8 (s, $CO\underline{C}(CH_3)_3$), 38.0 (t, C-6), 26.5 (q, $COC(\underline{CH_3})_3$) ppm.

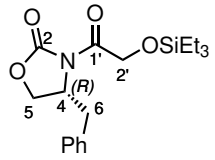
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{15}H_{20}NO_3$ 262.1438, found 262.1435.

IR (ATR): ν_{max} = 2962, 2918, 1774, 1683, 1482, 14 554, 1346, 1188 cm^{-1}.

$[\alpha]_D^{25}$**:** -43.1° ($c = 1.0$; $CHCl_3$).

(*R*)-4-Benzyl-3-(2-((triethylsilyl)oxy)acetyl)oxazolidin-2-one (40)

exp: 8
DL331



Glycolic acid (171 mg, 2.26 mmol) was added portionwise to a solution of NaH (60 wt − %, 112 mg, 2.82 mmol) in Et_2O (4.51 mL) at 0 °C, resulting in strong gas formation. After stirring for 20 min, Et_3N (315 µL, 2.37 mmol) was added, leading to a thick slurry, which was dissolved by dropwise addition of Et_3SiCl (347 µL, 2.36 mmol). The now colorless suspension was stirred at r.t. for 3 h and then cooled to −78 °C. PivCl (288 µL, 2.14 mmol) was added and the mixture stirred for 60 min.

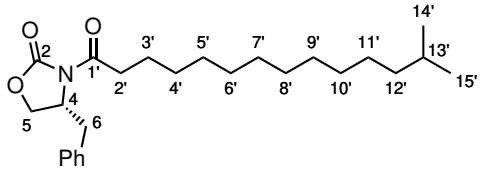
Meanwhile, oxazolidinone **36** (200 mg, 1.13 mmol) was dissolved in THF (4.50 mL), cooled to −78 °C and treated with *n*-BuLi (827 µL, 1.5 M in hexanes, 1.24 mmol). The yellow solution was stirred at −78 °C for 30 min and then added to the first reaction *via* double-tipped needle. The mixture was stirred at −78 °C for 60 min, then the cooling bath was removed and the mixture slowly warmed to r.t. over 1 h. After addition of citric acid solution (10 % in H_2O) the aqueous phase was extracted with Et_2O, the combined organic phase was washed with $NaHCO_3$ solution, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 10/1 → 6/1, eluting at 6/1) to yield **40** as a colorless oil (57.3 mg, 15 %).

^{1}H-NMR (300 MHz**, $CDCl_3$):** δ = 7.38 – 7.27 (m, 3 H, Ph-H), 7.24 – 7.17 (m, 2 H, Ph-H), 4.84 (s, 2 H, 2'-H), 4.69 (ddt, J = 3.3, 7.6, 9.6 Hz, 1 H, 4-H), 4.33 – 4.18 (m, 2 H, 5-H) 3.35 (dd, J = 13.4, 3.3 Hz, 1 H, 6-H), 2.80 (dd, J = 13.4, 9.5 Hz, 1 H, 6-H) 1.01 (t, J = 7.9 Hz, 9 H,$Si(CH_2C\underline{H_3})_3$), 0.69 (q, J = 7.9 Hz, 4 H, $Si(C\underline{H_2}CH_3)_3$) ppm.

The analytical data is consistent with literature reports.[175]

(*R*)-4-Benzyl-3-(13-methyltetradecanoyl)oxazolidin-2-one (42a)

exp: 9
SP137



13-Methyltetradecanoic acid **34** (2.50 g, 10.3 mmol) was dissolved in $SOCl_2$ (4.00 mL, 55.1 mmol) and stirred at r.t. for 16 h. After removal of the volatiles *in vacuo*, the acid chloride was dissolved in THF (10.0 mL).

(*R*)-4-Benzyloxazolidinone **36** (1.84 g, 10.4 mmol) was dissolved in THF (20.0 mL) and treated with *n*-BuLi (5.40 mL, 2.2 M in hexanes) at −78 °C. After stirring at −78 °C for 30 min, the acid chloride solution was added at −78 °C and the highly viscous mixture was allowed to warm to r.t. over 16 h. NH_4Cl solution was added and the aqueous phase extracted with EtOAc, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product

purified by flash chromatography (cyclohexane/EtOAc 50/1→10/1, eluting at 10/1) to yield **42a** as a brownish solid (2.03 g, 49 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.40 – 7.18 (m, 5 H, Ph-H), 4.67 (ddt, J = 10.2, 6.8, 3.4 Hz, 1 H, 4-H), 4.26 – 4.10 (m, 2 H, 5-H), 3.30 (dd, J = 13.3, 3.3 Hz, 1 H, 6-H), 3.08 – 2.69 (m, 3 H, 6-H, 2'-H), 1.81 – 1.60 (m, 2 H, 3-H), 1.51 (dp, J = 13.3, 6.6 Hz, 1 H, 13'-H), 1.43 – 1.20 (m, 20 H, 4'-H to 11'-H), 1.16 (dd, J = 8.0, 4.5 Hz, 2 H, 12'-H), 0.86 (d, J = 6.6 Hz, 6 H, 14'-H, 15'-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.6 (s, C-1'), 153.6 (s, C-2), 135.5 (s, C-Ph), 129.5, 129.1, 127.5 (3 d, C-Ph), 66.3 (t, C-5), 55.3 (d, C-4), 39.2, 38.1, 35.7, 30.1, 29.86, 29.82, 29.79, 29.6, 29.5, 29.3 (10t, C-2' to C-12', C-6), 28.1 (d, C-13'), 27.6, 24.4 (2t, C-2' to C-12', C-6), 22.8 (q, C-14', C-15') ppm.

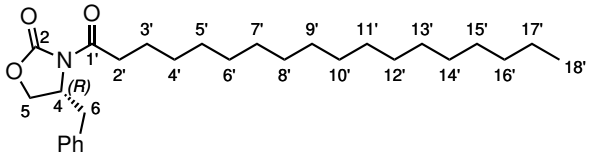
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{25}H_{40}NO_3$ 402.3003, found 402.3003.

IR (ATR): ν_{max} = 2923, 2852, 1780, 1699 cm^{-1}.

$[\alpha]_D^{25}$**:** -39.9° (c = 0.85; $CHCl_3$).

(*R*)-4-Benzyl-3-stearoyloxazolidin-2-one (42b)

exp: 10
DL598



Stearic acid (1.69 g, 5.93 mmol) was dissolved in $SOCl_2$ (1.80 mL, 24.8 mmol) and stirred at r.t for 16 h. After removal of the volatiles *in vacuo*, the acid chloride was dissolved in THF (12 mL).

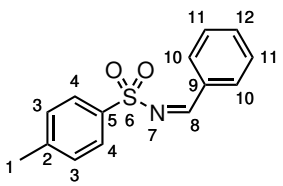
(*R*)-4-Benzyloxazolidinone **36** (1.00 g, 5.64 mmol) was dissolved in THF (12 mL) and treated with *n*-BuLi (3.00 mL, 2.3 M in hexanes) at −78 °C. After stirring at −78 °C for 30 min, the acid chloride solution was added at −78 °C and the highly viscous mixture was allowed to warm to r.t. over 3 h. Citric acid solution (10 wt − % in H_2O) was added, the aqueous phase extracted with TBME (3x), the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude recrystallized from hot MeOH to yield **42b** as a colorless solid (1.36 g, 55 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.13 (m, 5 H, Ph-H), 4.70 (ddt, J = 10.4, 6.9, 3.4 Hz, 1 H, 4-H), 4.28 – 4.13 (m, 2 H, 5-H), 3.32 (dd, J = 13.4, 3.3 Hz, 1 H, 6-H), 3.04 – 2.85 (m, 2 H, 2'-H), 2.79 (dd, J = 13.4, 9.6 Hz, 1 H, 6-H), 1.82 – 1.61 (m, 2 H, 3'-H to 17'-H), 1.46 – 1.19 (m, 32 H, 3'-H to 17'-H), 0.99 – 0.80 (m, 3 H, 18'-H) ppm.

The analytical data is consistent with literature reports.[176]

N-Benzylidene-4-methylbenzenesulfonamide (SI-2)

exp: 11
DL447



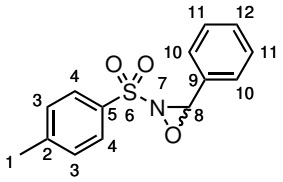
$BF_3{\cdot}OEt_2$ (3.14 mL, 25.5 mmol) was added dropwise to a suspension of 4-methylbenzenesulfonamide (50.0 g, 292 mmol) and benzaldehyde (33.8 g, 318 mmol) in toluene (500 mL) and the blue mixture refluxed

using a Dean-Stark-receiver for 16 h. After cooling to 0 °C NaOH solution (40 mL, 1 M) and H_2O (200 mL) were added and the aqueous phase was extracted with TBME. The combined organic phase was washed with H_2O, brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the residue recrystallized from hot cyclohexane/EtOAc to yield **SI-2** as a colorless solid (61.3 g, 81 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.02 (s, 1 H, 8-H), 7.93 – 7.26 (m, 9 H, Ar-H), 2.43 (s, 3 H, 1-H) ppm.

Davis' oxaziridine (SI-3)

exp: 12
DL568

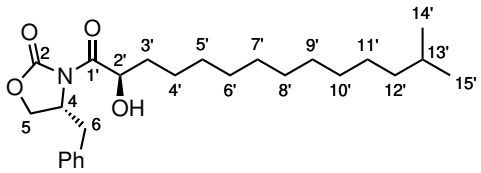


Benzyltriethylammonium chloride (878 mg, 3.86 mmol), aqueous $NaHCO_3$ solution (57.0 mL, 1.15 M, 65.6 mmol) and a suspension of *m*-CPBA(9.98 g, 40.5 mmol) in $CHCl_3$ (50 mL) were added to a solution of sulfimine **SI-2** (10.0 g, 38.6 mmol) in $CHCl_3$ (40.0 mL) at 0 °C. After stirring at 0 °C for 90 min, sat. $Na_2S_2O_5$ solution was added, the phases separated and the organic phase washed with sat. $NaHCO_3$ solution, brine and dried over $MgSO_4$, filtered and the volatiles removed *in vacuo*. Crystallization from warm EtOAc with cyclohexane afforded **SI-3** as a yellowish solid (5.23 g, 49 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.3 Hz, 2 H, Ar-H) 7.52 – 7.31 (m, 7 H, Ar-H), 5.45 (s, 1 H, 8-H), 2.43 (s, 3 H, 1-H) ppm.

(*R*)-4-Benzyl-3-((*R*)-2-hydroxy-13-methyltetradecanoyl)oxazolidin-2-one (45)

exp: 13
SP155



According to GP 3, the reaction of oxazolidinone **42a** (675 mg, 1.68 mmol) with KHMDS (5.00 mL, 3.50 mmol) and Davis' oxaziridine (833 mg, 3.00 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 50/1→10/1, eluting at 10/1), **45** as a brownish solid (480 mg, 68 %). The product was obtained as an inseparable mixture (3:1) with benzylidene-4-methylbenzenesulfonamide **SI-2**.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.42 – 7.30 (m, 3 H, Ph-H), 7.24 – 7.13 (m, 3 H, Ph-H), 4.99 (td, J = 7.9, 3.5 Hz, 1 H, 2'-H), 4.67 (ddt, J = 9.9, 6.6, 3.2 Hz, 1 H, 5-H), 4.33 – 4.16 (m, 2 H, 4-H), 3.45 (d, J = 7.9 Hz, 1 H, O-H), 3.31 (dd, J = 13.5, 3.3 Hz, 1 H, 6-H), 2.84 (dd, J = 13.5, 9.4 Hz, 1 H, 6-H), 1.70 – 1.38 (m, 4 H, 3'-H to 13'-H), 1.40 – 1.19 (m, 16 H, 3'-H to 13'-H), 1.20 – 1.01 (m, 2 H, 3'-H to 13'-H), 0.86 (d, J = 6.6 Hz, 6 H, 14'-H, 15'-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 175.2 (s, C-1'), 153.3 (s, C-2), 134.9 (s, C-Ph), 129.6, 129.2, 127.6 (3d, C-Ph), 71.0 (d, C-2'), 67.0 (t, C-4), 55.7 (d, C-5), 39.2 (t, C-12'), 37.6 (t, C-6), 34.4, 30.1, 29.82, 29.77, 29.7, 29.6, 29.4 (7t, C-3' to C-11'), 28.1 (d, C-13'), 27.5, 25.4 (2t, C-3' to C-11'), 22.8 (C-14', C-15') ppm.

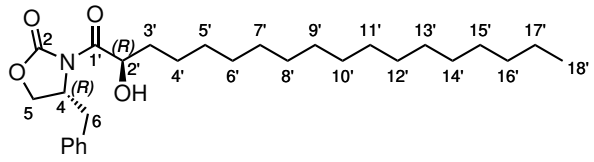
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{25}H_{40}NO_4$ 418.2952, found 418.2952.

IR (ATR): ν_{max} = 3516, 2924, 2853, 1783, 1698 cm^{-1}.

$[\alpha]_D^{25}$**:** -35.1° (c = 0.81; $CHCl_3$).

(*R*)-4-Benzyl-3-((*R*)-2-hydroxyoctadecanoyl)oxazolidin-2-one (46)

exp: 14
DL565



According to GP 3, the reaction of oxazolidinone **42b** (400 mg, 901 µmol) with KHMDS (3.22 mL, 2.25 mmol) and Davis' oxaziridine (745 mg, 2.70 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 →50/50, eluting at 75/25), **46** as a yellowish oil (128 mg, 31 %). The product was obtained as an inseparable mixture (1:3) with benzylidene-4-methylbenzenesulfonamide **SI-2**.

^{1}**H-NMR (**300 MHz**, $CDCl_3$**):** δ = 7.36 – 7.28 (m, 3 H, Ph-H), 7.23 – 7.19 (m, 2 H, Ph-H), 5.03 (dd, J = 8.0, 3.5 Hz, 1 H, 2'-H), 4.67 (ddt, J = 9.8, 6.6, 3.3 Hz, 1 H, 5-H), 4.27 – 4.24 (m, 1 H, 4-H), 3.32 (dd, J = 13.4, 3.3 Hz, 1 H, 6-H), 2.84 (dd, J = 13.5, 9.4 Hz, 1 H, 6-H), 1.75 – 1.45 (m, 2 H, 3'-H to 17'-H), 1.38 – 1.17 (m, 28 H, 3'-H to 17'-H), 0.95 – 0.80 (m, 3 H, 18'-H) ppm.

^{13}**C-NMR (**126 MHz**, $CDCl_3$**):** δ = 173.6 (s, C-1'), 153.6 (s, C-2), 135.5 (s, C-Ph), 129.6, 129.2, 127.5 (3t, C-Ph), 76.5 (d, C-2'), 66.3 (t, C-4), 55.3 (d, C-5), 38.1 (t, C-6), 35.7 (t, C-3'), 32.1 (t, C-4' to C-17') 30.1, 29.84, 29.81, 29.77, 29.7, 29.6, 29.5, 29.3 (8t, C-4' to C-17'), 24.4, 22.8 (2t, C-4' to C-17'), 14.3 (C-18') ppm.

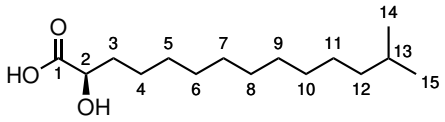
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{28}H_{46}NO_4$ 460.3421, found 460.3413.

IR (ATR) ν_{max}**:** 2922, 2852, 1780, 1698, 1459, 1385, 1350, 1212, 1167 cm^{-1}.

$[\alpha]_D^{25}$**:** +19.4° (c = 1.0; $CHCl_3$).

(*R*)-2-Hydroxy-13-methyltetradecanoic acid (43)

exp: 15
SP165



According to GP 4, the reaction of oxazolidinone **45** (30.0 mg, 71.8 µmol) with LiOH (5.30 mg, 221 µmol) and H_2O_2 (45.5 µL, 446 µmol) yielded, after flash chromatography (cyclohexane/EtOAc + 0.1 % AcOH 100/0→50/50, eluting at 60/40), **43** as a colorless wax (12.0 mg, 65 %).

Alternatively, the reaction of acetonide **SI-7** (48 mg, 160 µmol) with 1 M aq. HCl (2.10 mL, 2.10 mmol) according to GP 9 yielded, after flash chromatography (cyclohexane/EtOAc + 0.1 % HOAc 100/0 → 0/100, eluting at 0/100), **43** as a colorless wax (24.6 mg, 59 %).

exp:16
DL595

^{1}**H-NMR (**300 MHz**, $CDCl_3$**):** δ = 4.27 (dd, J = 7.5, 4.3 Hz, 1 H, 2-H), 1.94 – 1.78 (m, 1 H, 3-H), 1.78 – 1.60 (m, 1 H, 3-H), 1.58 – 1.41 (m, 3 H, 4-H to 11-H,13-H), 1.40 – 1.20 (m, 15 H, 4-H to 11-H), 1.20 – 1.07 (m, 2 H, 12-H), 0.86 (d, J = 6.6 Hz, 6 H, 14-H, 15-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 180.0 (s, C-1), 70.4 (d, C-2), 39.2 (t, C-12), 34.4 (t, C-3), 30.08, 30.06, 29.84, 29.79, 29.7, 29.6, 29.4 (7t, C-4 to C-11), 28.1 (d, C-13), 27.6, 24.9 (2t, C-4 to C-11), 22.8 (q, C-14, C-15) ppm.

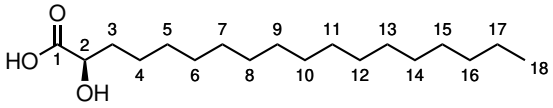
HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{15}H_{29}O_3$ 257.2122, found 257.2120.

IR (ATR): ν_{max} = 3516, 2924, 1783, 1698 cm^{-1}.

$[\alpha]_D^{25}$**:** -35.1° ($c = 0.81$; $CHCl_3$).

(*R*)-2-Hydroxyoctadecanoic acid (44)

exp: 17
DL571



According to GP 4, the reaction of oxazolidinone **46** (11.6 mg, 25.1 µmol) with LiOH (1.20 mg, 50.3 µmol) and H_2O_2 (18.0 µL, 176 µmol) yielded, after flash chromatography (cyclohexane/EtOAc + 0.1 % AcOH 100/0→50/50, eluting at 60/40), **44** as a colorless solid (1.08 mg, 15 %).

Alternatively, the reaction of acetonide **SI-9** (48 mg, 141 µmol) with 1 M aq. HCl (1.06 mL, 1.06 mmol) according to GP 9 yielded, after flash chromatography (cyclohexane/EtOAc + 0.1 % HOAc 100/0 → 0/100, eluting at 0/100), **44** as a colorless wax (33.4 mg, 79 %). exp:18 DL593

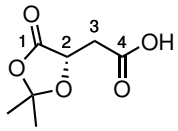
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 4.16 (dd, J = 7.5, 4.1 Hz, 1 H, 2-H), 1.85 – 1.75 (m, 1 H, 3-H), 1.69 – 1.59 (m, 1 H, 3-H), 1.49 – 1.35 (m, 2 H, 4-H to 17-H), 1.24 (d, J = 2.6 Hz, 26 H, 4-H to 17-H), 0.87 (t, J = 7.0 Hz, 3 H, 18-H) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 177.6 (C-1), 70.3 (C-2), 34.4 (C-3), 32.0, 29.82, 29.80, 29.78, 29.7, 29.6, 29.5, 29.5, 25.0, 22.8 (10t, C-4 to C-17), 14.2 (C-18) ppm.

HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{18}H_{35}O_3$ 299.2581, found 299.2580.

(*S*)-2-(2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (48)

exp: 19
MZ026



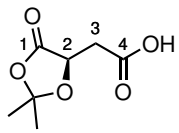
PPTS (3.10 g, 29.8 mmol) was added to a solution of L-malic acid (20 g, 149 mmol) in 2,2-dimethoxypropane (150 mL, 1.69 mol) and the two-phase mixture stirred at r.t. for 24 h. The volatiles were removed *in vacuo* and the crude product purified by filtration over a silica pad (cyclohexane/EtOAc 4/1 → 1/1). The solid was dissolved in Et_2O, precipitated with cyclohexane, filtered and washed with pentane to yield **48** as a colorless powder (21.5 g, 83 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.44 (br. s, 1 H, $CO_2\underline{H}$), 4.71 (dd, J = 6.4, 3.9 Hz, 1 H, 2-H), 2.99 (dd, J = 17.3, 3.9 Hz, 1 H, 3-H), 2.85 (dd, J = 17.3, 6.5 Hz, 1 H, 3-H), 1.61, 1.56 (2s, 2x 3 H,C($C\underline{H}_3$)$_2$) ppm.

The analytical data is consistent with literature reports.[82]

(*R*)-2-(2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (50)

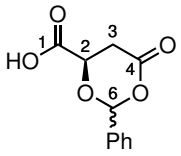
exp: 20
MZ022



PPTS (3.10 g, 29.8 mmol) was added to a solution of D-malic acid (20.0 g, 149 mmol) in 2,2-dimethoxypropane (150 mL, 1.69 mol) and the two-phase mixture was stirred at r.t. for 48 h. The volatiles were removed *in vacuo* and the crude product purified by filtration over a silica pad (cyclohexane/EtOAc 4/1 → 1/1). The solid was dissolved in Et_2O, precipitated with cyclohexane, filtered and washed with pentane to yield **48** as a colorless powder (14.3 g, 55 %).

(*R*)-6-Oxo-2-phenyl-1,3-dioxane-4-carboxylic acid (51)

exp: 21
MZ025



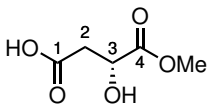
PPTS (77.6 mg, 746 µmol) was added to a solution of D-malic acid (1.00 g, 7.46 mmol) and (dimethoxymethyl)benzene (11.4 g, 74.6 mmol) in CH_2Cl_2 (35.0 mL) and the mixture was stirred at r.t. for 24 h. The volatiles were removed *in vacuo* and the residue filtered over a silica pad (cyclohexane/EtOAc 4/1 → 1/1). The crude product was purified by flash chromatography (cyclohexane/EtOAc 4/1) to yield **51** as a colorless powder (318 mg, 19 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.64 (br. s, 1 H, $CO_2\underline{H}$), 7.55 – 7.38 (m, 5 H, Ph-H), 6.41 (d, J = 1.3 Hz, 1 H, 6-H), 4.79 (ddd, J = 6.7, 3.9, 1.5 Hz, 1 H, 2-H), 3.12 (dd, J = 17.5, 3.9 Hz, 1 H, 3-H), 2.98 (dd, J = 17.6, 6.6 Hz, 1 H, 3-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.7 (s, C-4), 171.9 (s, C-1), 133.9 (s, C-Ph) 130.9, 128.8, 127.0 (3d, C-Ph), 103.8 (d, C-6), 71.8 (d, C-2), 60.7 (t, C-3) ppm.

(*R*)-3-Hydroxy-4-methoxy-4-oxobutanoic acid (52)

exp: 22
DL684



D-Malic acid (56.5 g, 421 mmol) was cooled to 0 °C and trifluoroacetic anhydride (128 mL, 927 mmol) was added dropwise over 15 min. The colorless suspension was stirred at 0 °C for 2 h, after which the volatiles were removed *in vacuo* at 0 °C to yield a colorless solid.

MeOH was added to this solid at 0 °C over 20 min and the solution was stirred at 0 °C for 90 min. Stirring was stopped, the solution was allowed to warm to r.t. overnight and the volatiles were removed *in vacuo*. The solid was dissolved in 40 °C-warm EtOAc (250 mL) and cyclohexane (75 mL) was added until the solution turned opaque. The suspension was stored in the freezer overnight, the resulting solid filtered off and washed with pentane to yield **52** as a colorless solid (35.4 g, 56 %).

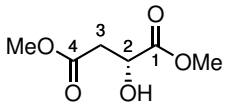
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.52 (dd, J = 6.1, 4.4 Hz, 1 H, 3-H), 3.83 (s, 3 H, OC<u>H</u>$_3$), 2.93 (dd, J = 16.7, 4.3 Hz, 1 H, 1-H), 2.85 (dd, J = 16.7, 6.3 Hz, 1 H, 1-H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 175.2 (s, C-1), 173.7 (s, C-4), 67.1 (d, C-3), 53.2 (q, O<u>C</u>H$_3$), 38.4 (t, C-2) ppm.

The analytical data is consistent with literature reports.[84]

Dimethyl (*R*)-2-hydroxysuccinate (53)

exp: 23
DL684



Diester **53**, a side product in the synthesis of **52**, was isolated *via* evaporation of the mother liquor as a yellowish liquid (25.0 g, 36 %)

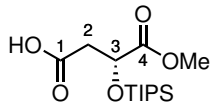
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.45 (dd, J = 6.5, 4.4 Hz, 1 H, 2-H), 3.69, 3.61 (2s, 2x 3 H, OC<u>H</u>$_3$), 2.77 (dd, J = 16.3, 4.4 Hz, 1 H, 1-H), 2.70 (dd, J = 16.4, 6.4 Hz, 1 H, 1-H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 173.7 (s, C-1), 171.1 (s, C-4), 67.2 (d, C-2), 52.7, 51.9 (2d, O<u>C</u>H$_3$), 38.4 (t, C-3) ppm.

The analytical data is consistent with literature reports.[177]

(*R*)-4-Methoxy-4-oxo-3-((triisopropylsilyl)oxy)butanoic acid (54)

exp: 24
DL686



Imidazole (41.4 g, 607 mmol) and TIPSCl (90.3 mL) were added dropwise to a solution of carboxylic acid **52** (30.0 g, 203 mmol) in DMF (100 mL) while cooling in a r.t. water bath. After stirring at r.t. for 16 h, the now opaque suspension was treated with aqueous K_2CO_3 solution (5 M, 141 mL, 708 mmol) dropwise over 40 min, which resulted in gas formation. The mixture was stirred for 24 h, the phases separated and the aqueous phase extracted with TBME (3x). The aqueous phase was acidified to a pH below 2 and again extracted with TBME (3x). The combined organic phase of the acidic extraction was washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield **54** as a colorless liquid (53.0 g, 86 %).

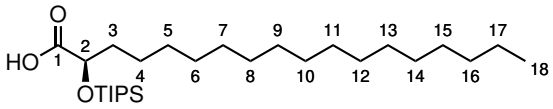
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.12 (br. s, 1 H, CO_2<u>H</u>), 4.72 (td, J = 6.0, 1.2 Hz, 1 H, 3-H), 3.73 (s, 3 H, OC<u>H</u>$_3$), 2.91 – 2.69 (m, 2 H, 2-H) 1.16 – 0.92 (m, 21 H, SiCH(C<u>H</u>$_3$)$_2$, SiC<u>H</u>(CH$_3$)$_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 175.8 (s, C-1), 172.7 (s, C-4), 69.3 (d, C-3), 52.2 (q, O<u>C</u>H$_3$), 40.5 (t, C-2), 17.95, 17.92 (2q, SiCH(<u>C</u>H$_3$)$_2$), 12.4 (d, Si<u>C</u>H(CH$_3$)$_2$), ppm.

HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{14}H_{27}O_5Si$ 303.1622, found 303.1630.

(*S*)-5-Heptyl-2,2-dimethyl-1,3-dioxolan-4-one (55)

exp: 25
DL463



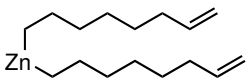
According to GP 6, the reaction of carboxylic acid **48** (100 mg, 574 µmol) with CITU (344 mg, 631 µmol), NMM (140 µL, 1.26 mmol), $NiCl_2$·diglyme (25.2 mg, 114 µmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (61.6 mg, 230 µmol), $ZnCl_2$ (164 mg, 1.21 mmol) and pentylmagnesium bromide (3.16 mL, 2.53 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 90/10), **55** as a colorless oil (30.2 mg, 25 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.38 (dd, J = 7.2, 4.4 Hz, 1 H, 2-H), 1.93 – 1.77 (m, 1 H, 3-H), 1.77 – 1.62 (m, 1 H, 3-H), 1.59, 1.53 (2s, 2x 3 H, $C(\underline{CH_3})_2$), 1.51 – 1.37 (m, 2 H, 4-H to 8-H), 1.37 – 1.21 (m, 9 H, 4-H to 8-H), 0.91 – 0.81 (m, 3 H, 9-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.5 (s, C-1), 110.5 (s, $\underline{C}(CH_3)_2$), 74.3 (d, C-2), 31.8, 31.7, 29.3, 29.2 (4t, C-3 to C-8), 27.3, 25.9 (2q, $C(\underline{C}H_3)_2$), 25.0, 22.7 (2t, C-3 to C-8), 14.2 (q, C-9) ppm.

Di(oct-7-en-1-yl)zinc (SI-4)

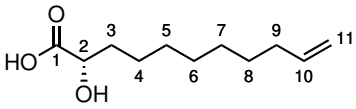
exp: 26
DL732



According to GP 5, reaction of $ZnCl_2$ (4.50 g, 33.0 mmol), Mg (4.41 g, 181 mmol) and 8-bromooct-1-ene (28.4 g, 148 mmol) yielded **SI-4** as a gray solution in THF, which was directly used in the next step.

(*S*)-2-Hydroxyundec-10-enoic acid (56)

exp: 27
DL669



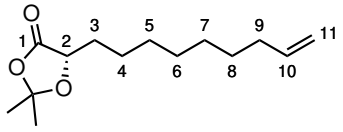
According to GP 9, the reaction of acetonide **SI-5** (100 mg, 416 µmol) with HCl (5.00 mL, 5.00 mmol) yielded **56** as a colorless oil (84.1 mg, quant.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.98 – 5.56 (m, 2 H, 10-H, O-H), 5.06 – 4.82 (m, 2 H, 11-H), 4.26 (dd, J = 7.5, 4.2 Hz, 1 H, 2-H), 2.03 (q, J = 6.8 Hz, 2 H, 3-H, 9-H), 1.95 – 1.76 (m, 1 H, 9-H) 1.76 – 1.60 (m, 1 H, 3-H), 1.54 – 1.14 (m, 14 H, 4-H to 8-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 179.6 (s, C-1), 139.3 (d, C-10), 114.3 (t, C-11), 70.4 (d, C-2), 34.3 (d, C-3), 33.9 (t, C-9), 29.4, 29.3, 29.1, 29.0, 24.9 (5t, C-4 to C-8) ppm.

(*S*)-2,2-Dimethyl-5-(non-8-en-1-yl)-1,3-dioxolan-4-one (SI-5)

exp: 28
DL638



According to GP 6, the reaction of carboxylic acid **48** (3.00 g, 17.2 mmol) with CITU (10.3 g, 19.0 mmol), NMM (4.17 mL, 37.9 mmol), $NiCl_2$·diglyme (378 mg, 1.72 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (924 mg, 3.45 mmol), and di(oct-7-en-1-yl)zinc **SI-4** (213 mL, 36.2 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 80/20, eluting at 90/10), **SI-5** as a colorless liquid (805 mg, 19 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.79 (ddt, J = 16.9, 10.2, 6.7 Hz, 1 H, 10-H), 5.13 – 4.88 (m, 2 H, 11-H), 4.37 (dd, J = 7.1, 4.4 Hz, 1 H, 2-H), 2.02 (q, J = 6.4 Hz, 2 H, 9-H), 1.93 – 1.79 (m, 1 H, 3-H), 1.77 – 1.61 (m, 1 H, 3-H), 1.59, 1.52 (2s, 2x 3 H, $C(C\underline{H_3})_2$), 1.49 – 1.18 (m, 10 H, 4-H to 8-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.5 (s, C-1), 139.2 (d, C-10), 114.3 (t, C-11), 110.4 (s, $\underline{C}(CH_3)_2$), 74.2 (d, C-2), 33.9 (t, C-9), 31.7 (t, C-3), 29.3, 29.2, 29.1, 29.0 (4t, C-4 to C-7), 27.3, 25.9 (2q, $C(\underline{C}H_3)_2$), 25.0 (t, C-8) ppm.

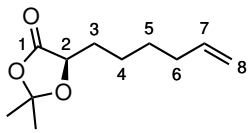
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{14}H_{24}O_3Na$ 263.1618, found 263.1607.

IR (ATR): ν_{max} = 2926, 2855, 1794, 1386, 1265, 1237, 1218, 1126 cm^{-1}.

$[\alpha]_D^{25}$**:** -1.78° (c = 1.1; $CHCl_3$).

(*R*)-5-(Hex-5-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-one (57)

exp: 29
MZ036



According to GP 6, the reaction of carboxylic acid **50** (50.0 mg, 287 µmol) with CITU (172 mg, 316 µmol), NMM (70.0 µL, 630 µmol), $NiCl_2$·diglyme (12.7 mg, 57.8 µmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (30.6 mg, 114 µmol), $ZnCl_2$ (82.1 mg, 617 µmol) and pent-4-en-1-ylmagnesium bromide (2.52 mL, 1.26 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 90/10), **57** as a colorless oil (24.2 mg, 42 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.80 (ddt, J = 16.9, 10.1, 6.7 Hz, 1 H, 7-H), 5.12 – 4.83 (m, 2 H, 8-H), 4.39 (dd, J = 7.2, 4.3 Hz, 1 H, 2-H), 2.18 – 2.02 (m, 2 H, 6-H), 1.97 – 1.80 (m, 1 H, 3-H), 1.80 – 1.65 (m, 1 H, 3-H), 1.60, 1.54 (2s, 2x 3 H, $C(C\underline{H_3})_2$), 1.51 – 1.35 (m, 4 H, 4-H, 5-H), ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.5 (s, C-1), 138.7 (d, C-7), 114.8 (t, C-8), 110.6 (s, $\underline{C}(CH_3)_2$), 74.2 (d, C-2), 33.6 (t, C-6), 31.5 (t, C-3), 28.6 (t, C-5), 27.3, 25.9 (2q, $C(\underline{C}H_3)_2$,) 24.5 (t, C-4) ppm.

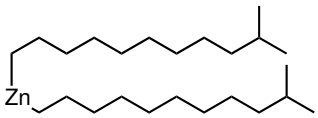
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{11}H_{18}NaO_3$ 221.1148, found 221.1144.

IR (ATR): ν_{max} = 2993, 2925, 2856, 1792, 1263, 12 191 120 cm^{-1}.

$[\alpha]_D^{25}$**:** +1.62° (c = 1.1; $CHCl_3$).

Bis(10-methylundecyl)zinc (SI-6)

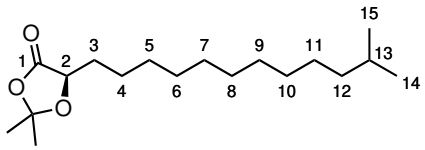
exp: 30
DL612



According to GP 5, reaction of $ZnCl_2$ (2.45 g, 18.0 mmol), Mg (1.05 g, 43.2 mmol), 1,2-dibromoethane (308 µL, 3.60 mmol) and 1-bromo-10-methylundecane **33** (8.96 g, 36.0 mmol) yielded **SI-6** as a gray solution in THF, which was directly used in the next step.

(*R*)-2,2-Dimethyl-5-(11-methyldodecyl)-1,3-dioxolan-4-one (SI-7)

exp: 31
DL614

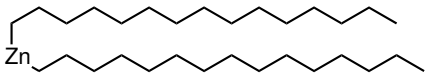


According to GP 6, the reaction of carboxylic acid **50** (1.65 g, 8.90 mmol) with CITU (5.34 g, 9.79 mmol), NMM (2.15 mL, 19.6 mmol), $NiCl_2$·diglyme (391 mg, 1.78 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (956 mg, 3.56 mmol) and bis(10-methylundecyl)zinc **SI-6** (142 mL, 17.8 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 97/3 → 81/19, eluting at 96/4), **SI-7** as a yellowish oil (833 mg, 32 %).

^{1}H-NMR (600 MHz**, CDCl$_3$):** δ = 4.37 (dd, J = 7.2, 4.3 Hz, 1 H, 2-H), 1.91 – 1.82 (m, 1 H, 3-H), 1.75 – 1.67 (m, 1 H, 3-H), 1.59, 1.53 (2s, 2x 3 H, C(C$\underline{H_3}$)$_2$), 1.52 – 1.36 (m, 1 H, 4-H to 13-H), 1.35 – 1.19 (m, 14 H, 4-H to 13-H), 0.86 (d, J = 7.2 Hz, 6 H, 14-H, 15-H) ppm.

Dipentadecylzinc (SI-8)

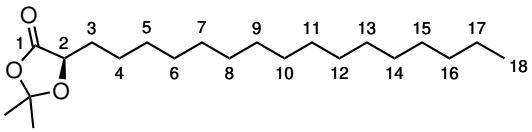
exp: 32
DL765



According to GP 5, reaction of $ZnCl_2$ (1.00 g, 7.34 mmol), Mg (891 mg, 36.7 mmol), 1,2-dibromoethane (126 µL, 1.47 mmol) and 1-bromopentadecane (7.27 g, 25.0 mmol) yielded **SI-8** as a gray solution in THF, which was directly used in the next step.

(*R*)-5-Hexadecyl-2,2-dimethyl-1,3-dioxolan-4-one (SI-9)

exp: 33
DL590



According to GP 6, the reaction of carboxylic acid **50** (100 mg, 574 µmol) with CITU (344 mg, 631 µmol), NMM (138 µL, 1.26 mmol), $NiCl_2$·diglyme (25.2 mg, 115 µmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (61.7 mg, 230 mmol) and dipentadecylzinc **SI-8** (11.5 mL, 1.44 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 50/50, eluting at 90/10), **SI-9** as a yellowish oil (107 mg, 55 %).

^{1}H-NMR (600 MHz**, CDCl$_3$):** δ = 4.38 (dd, J = 7.2, 4.3 Hz, 1 H, 2-H), 1.91 – 1.82 (m, 1 H, 3-H), 1.76 – 1.68 (m, 1 H, 3-H), 1.60, 1.54 (2s, 2x 3 H, C(C$\underline{H_3}$)$_2$), 1.51 – 1.38 (m, 2 H, 4-H to 17-H), 1.38 – 1.18 (m, 32 H, 4-H to 17-H), 0.88 (t, J = 7.0 Hz, 3 H, 18-H) ppm.

^{13}C-NMR (151 MHz**, CDCl$_3$):** δ = 173.6 (s, C-1), 110.5 (s, $\underline{C}(CH_3)_2$), 74.3 (d, C-2), 32.1 (t, C-17), 31.7 (t, C-3), 29.9, 29.81, 29.77, 29.7, 29.54, 29.52, 29.4 (7t, C-5 to C-16), 27.3, 26.0 (2q, C($\underline{C}H_3)_2$), 25.0 (C-4), 22.9 (C-17), 14.3 (C-18) ppm.

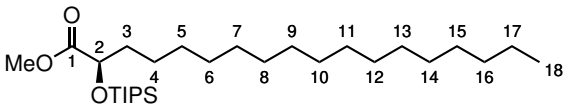
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{21}H_{41}O_3$ 341.3050, found 341.3042.

IR (ATR): ν_{max} = 2921, 2852, 1796, 1456, 1385, 1264, 1115 cm^{-1}.

$[\alpha]_D^{25}$**:** +1.22° (c = 1.0; $CHCl_3$).

Methyl (*R*)-2-((triisopropylsilyl)oxy)octadecanoate (SI-10)

exp: 34
DL766



Carboxylic acid **54** (1.00 g, 3.28 mmol) and DIC (496 µL, 3.61 mmol) were added to a yellow solution of TCNHPI (988 mg, 3.28 mmol) and 4-DMAP (40.1 mg, 328 µmol) in CH_2Cl_2 (32.9 mL) and the now orange suspension dissolved while stirring at r.t. for 10 min. The volatiles were removed *in vacuo*, the remaining solid treated with a light green solution of $NiCl_2 \cdot$ glyme (144 mg, 659 µmol) and 4,4′-di-*tert*-butyl-2,2′-dipyridine (352 mg, 1.31 mmol) in DMF (32.9 mL) and the grey-green solution stirred at r.t. for 5 min. Freshly prepared zinc-reagent **SI-8** (65.7 mL of a 0.11 M solution, 7.23 mmol) was added dropwise using a waterbath. The dark green suspension was stirred at r.t. for 24 h and cooled to 0 °C. Cyclohexane and 1 M HCl were added, the aqueous phase extracted with cyclohexane, the combined organic phase washed with H_2O, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 98/2) to yield **SI-10** as a colorless oil (841 mg, 54 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.35 (t, J = 5.8 Hz, 1 H, 2-H), 3.70 (s, 3 H, OC$\underline{H}_3$), 1.71 (dd, J = 7.8, 6.0 Hz, 2 H, 3-H), 1.25 (d, J = 1.7 Hz, 40 H, 4-H to 17-H, SiC$\underline{H}(CH_3)_2$), 1.16 – 0.99 (m, 23 H, SiCH(C$\underline{H}_3)_2$), 0.93 – 0.80 (m, 3 H, 18-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.5 (s, C-1), 72.6 (d, C-2), 51.7 (q, O$\underline{C}H_3$), 35.9, 32.1, 29.9, 29.82, 29.78, 29.73, 29.68, 29.63, 29.59, 29.52, 24.6, 22.8 (10t, C-4 to C-17), 18.04, 18.02 (2q, SiCH($\underline{C}H_3)_2$), 14.3 (q, C-18), 12.4 (d, Si$\underline{C}H(CH_3)_2$) ppm.

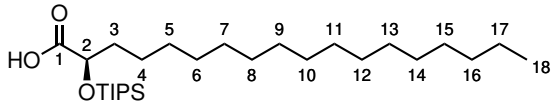
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{28}H_{59}O_3Si$ 471.4228, found 471.4222.

IR (ATR) ν_{max}: 2922, 2853, 1456, 1144 cm^{-1}.

$[\alpha]_D^{25}$: +7.19° (c = 1.0; $CHCl_3$).

(*R*)-2-((triisopropylsilyl)oxy)octadecanoic acid (59)

exp: 35
DL767



An aqueous solution of LiOH (4 M, 4.25 mL) was added to a solution of methyl ester **SI-10** (800 mg, 1.70 mmol) in THF/MeOH (1/1, 17.0 mL) at 0 °C and the clear solution stirred at r.t. for 16 h. After cooling to 0 °C, 1 M HCl was added dropwise until the pH was below 2. The aqueous phase was extracted with EtOAc, the combined organic phase washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 90/10) to yield **59** as a yellowish oil (180 mg, 23 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.16 (dd, J = 7.1, 4.2 Hz, 1 H, 2-H), 1.88 – 1.74 (m, 1 H, 3-H), 1.64 (tdd, J = 13.5, 7.1, 4.4 Hz, 1 H, 3-H), 1.55 – 1.19 (m, 40 H, 4-H to 17-H, SiC$\underline{H}(CH_3)_2$), 1.08 (d, J = 7.4 Hz, 19 H, SiCH(C$\underline{H}_3)_2$), 0.93 – 0.79 (m, 3 H, 18-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 175.7 (s, C-1), 71.2 (d, C-2), 34.5 (t, C-3), 32.1, 29.85, 29.81, 29.79, 29.7, 29.6, 29.5, 25.1, 22.8 (9t, C-4 to C-17), 17.8 (q, SiCH($\underline{C}H_3)_2$), 14.3 (q, C-18), 12.0 (d, Si$\underline{C}H(CH_3)_2$) ppm.

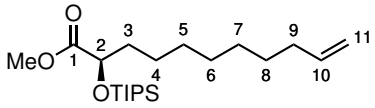
HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{27}H_{55}O_3Si$ 455.3915, found 455.3932.

IR (ATR) ν_{max}: 2922, 2852, 1713, 1464, 1258, 1215 cm^{-1}.

$[\alpha]_D^{25}$**:** +2.99° ($c = 1.0$; $CHCl_3$).

Methyl (*R*)-2-((triisopropylsilyl)oxy)undec-10-enoate (60)

exp: 36
DL733



According to GP 6, the reaction of carboxylic acid **54** (5.00 g, 16.4 mmol) with CITU (9.85 g, 18.1 mmol), NMM (3.97 mL, 36.1 mmol), $NiCl_2$·diglyme (722 mg, 3.28 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridine (1.76 g, 6.57 mmol) and di(oct-7-en-1-yl)zinc **SI-4** (164 mL, 32.9 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 90/10, eluting at 94/6), **60** as a colorless liquid (1.97 g, 32 %).

^{1}**H-NMR** (300 MHz, $CDCl_3$)**:** δ = 5.78 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H, 10-H), 5.03 – 4.87 (m, 2 H, 11-H), 4.34 (t, J = 5.8 Hz, 1 H, 2-H), 3.69 (s, 3 H, $OC\underline{H}_3$), 2.01 (q, J = 7.1 Hz, 2 H, 9-H), 1.77 – 1.63 (m, 2 H, 3-H), 1.48 – 1.20 (m, 12 H, 4-H to 8-H), 1.16 – 0.94 (m, 23 H, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$) ppm.

^{13}**C-NMR** (75 MHz, $CDCl_3$)**:** δ = 174.4 (s, C-1), 139.2 (d, C-10), 114.2 (t, C-11), 72.6 (d, C-2), 51.6 (q, $O\underline{C}H_3$), 35.8 (t, C-3), 33.9 (t, C-9), 29.5, 29.4, 29.1, 29.0, 24.6 (5t, C-4 to C-8), 18.01, 17.98 (2q, $SiCH(\underline{C}H_3)_2$), 12.4 (d, $Si\underline{C}H(CH_3)_2$) ppm.

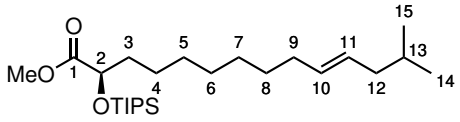
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{18}H_{37}O_3Si$ 329.2506, found 329.2516.

IR (ATR): ν_{max} = 2926, 2865, 1758, 1463, 1195, 1144 cm^{-1}.

$[\alpha]_D^{25}$**:** +9.21° ($c = 3.0$; $CHCl_3$).

Methyl (*R*,*E*)-13-methyl-2-((triisopropylsilyl)oxy)tetradec-10-enoate (SI-11)

exp: 37
DL735



According to GP 7, the reaction of alkene **60** (500 mg, 1.35 mmol) with HG II (33.8 mg, 54.0 µmol and 4-methylpent-1-ene (3.41 mL, 27.0 mmol)) yielded, after flash chromatography (cyclohexane/EtOAc 97/3), **SI-11** as a greenish liquid (563 mg, 98 %).

^{1}**H-NMR** (300 MHz, $CDCl_3$)**:** δ = 5.44 – 5.25 (m, 2 H, 10-H, 11-H), 4.35 (t, J = 5.8 Hz, 1 H, 2-H), 3.71 (s, 3 H, $OC\underline{H}_3$), 2.05 – 1.80 (m, 5 H, 3-H to 9-H), 1.79 – 1.65 (m, 2 H, 3-H to 9-H) 1.58 (hept, J = 6.7 Hz, 1 H, 13-H), 1.40 – 1.21 (m, 12 H, 3-H to 9-H, 12-H), 1.16 – 1.00 (m, 23 H, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$), 0.86 (d, J = 6.7 Hz, 6 H, 14-H, 15-H) ppm.

^{13}**C-NMR** (75 MHz, $CDCl_3$)**:** δ = 174.5 (s, C-1), 131.6, 129.1 (2d, C-10, C-11), 72.6 (d, C-2), 51.7 (q, $O\underline{C}H_3$), 42.2 (t, C-12), 35.9 (t, C-3), 32.8, 29.8, 29.6, 29.5, 29.2 (5t, C-4 to C-9), 28.6 (d, C-13), 24.6 (t, C-4 to C-9, C-12), 22.4 (q, C-14, C-15), 18.1, 18.0 (2q, $SiCH(\underline{C}H_3)_2$), 12.4 (d, $Si\underline{C}H(CH_3)_2$) ppm.

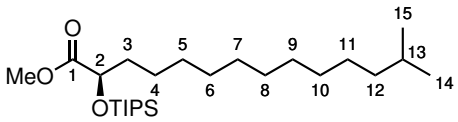
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{25}H_{51}O_3Si$ 427.3602, found 427.3605.

IR (ATR): ν_{max} = 2944, 2924, 2866, 1759, 1463, 1256, 1145 cm^{-1}.

$[\alpha]_D^{25}$**:** +8.42° ($c = 1.0$; $CHCl_3$).

Methyl (*R*)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanoate (SI-12)

exp: 38
DL736



According to GP 8, the reaction of alkene **SI-11** (550 mg, 1.29 mmol) with Pd/C (137 mg, 129 µmol) in H_2-atmosphere yielded **SI-12** as a colorless oil (535 mg, 97 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.35 (t, J = 5.8 Hz, 1 H, 2-H), 3.71 (s, 3 H, OC$\underline{H}_3$), 1.72 (dd, J = 13.6, 7.4 Hz, 2 H, 3-H), 1.61 – 1.40 (m, 2 H, 4-H to 11-H, 13-H), 1.40 – 1.18 (m, 21 H, 4-H to 11-H), 1.18 – 0.94 (m, 20 H, 12-H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.87 (d, J = 6.6 Hz, 6 H, 14-H, 15-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.5 (s, C-1), 72.6 (d, C-2), 51.7 (q, O$\underline{C}$H$_3$), 39.2 (t, C-12), 35.9 (t, C-3), 30.1, 29.8, 29.8, 29.7, 29.6, 29.6 (6t, C-4 to C-11), 28.1 (d, C-13), 27.6, 24.6 (2t, C-4 to C-11), 22.8 (q, C-14, C-15), 18.04, 18.02 (2q, SiCH(C$\underline{H}_3$)$_2$), 12.4 (d, Si$\underline{C}$H(CH$_3$)$_2$) ppm.

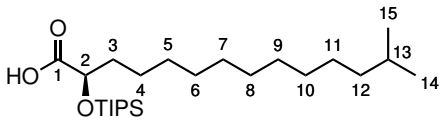
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{25}H_{53}O_3Si$ 429.3758, found 429.3759.

IR (ATR): ν_{max} = 2923, 2865, 2854, 1759, 1463, 1260, 1143 cm^{-1}.

$[\alpha]_D^{25}$**:** +10.0° (c = 1.0; $CHCl_3$).

(*R*)-13-Methyl-2-((triisopropylsilyl)oxy)tetradecanoic acid (61)

exp: 39
DL737



An aqueous solution of LiOH (4 M, 3.11 mL) was added to a solution of methyl ester **SI-12** (534 mg, 1.25 mmol) in THF/MeOH (1/1, 12.5 mL) at 0 °C and the clear solution stirred at r.t. for 16 h. After cooling to 0 °C, 1 M HCl was added dropwise until the pH was below 2. The aqueous phase was extracted with EtOAc, the combined organic phase washed with brine, dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield **61** as a yellowish oil (522 mg, quant.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.44 (dd, J = 5.7, 4.1 Hz, 1 H, 2-H), 1.96 – 1.66 (m, 2 H, 3-H), 1.64 – 1.39 (m, 3 H, 4-H to 11-H, 13-H), 1.39 – 0.97 (m, 44 H, 4-H to 12-H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.86 (d, J = 6.6 Hz, 6 H, 14-H, 15-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.9 (s, C-1), 72.7 (d, C-2), 39.2 (t, C-12), 35.1 (t, C-3), 30.1, 30.0, 29.82, 29.77, 29.75, 29.64, 29.58, 29.53 (8t, C-4 to C-11), 28.1 (d, C-13), 27.6, 23.7 (2t, C-4 to C-11), 22.8 (q, C-14, C-15), 17.99, 17.95 (2q, SiCH(C$\underline{H}_3$)$_2$), 12.2 (d, Si$\underline{C}$H(CH$_3$)$_2$)ppm.

HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{24}H_{49}O_3SI$ 413.3445, found 413.3455.

IR (ATR): ν_{max} = 2923, 2865, 1724, 1463, 1238, 1145, 1118 cm^{-1}.

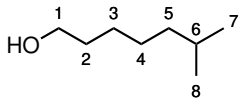
$[\alpha]_D^{25}$**:** -2.15° (c = 1.0; $CHCl_3$).

4.4 Synthesis of unnatural ceramides

4.4.1 Synthesis of the alkyne building blocks

6-Methylheptan-1-ol (62)

exp: 40
DL302



According to GP 1, the reaction of 4-bromobutan-1-ol (10.0 g, 65.3 mmol) with *i*-butylmagnesium bromide (42.5 mL, 85.0 mmol), *i*-propylmagnesium bromide (19.6 mL, 58.8 mmol) and Li_2CuCl_4 (13.1 mL, 1.31 mmol) yielded **62** as a colorless oil (6.35 g, 75 %).

b.p. = 84 – 86 °C (14.9 hPa).

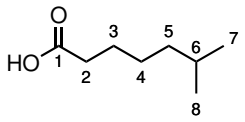
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.64 (t, J = 6.6 Hz, 2 H, 1-H), 1.64 – 1.43 (m, 3 H, 2-H, 6-H), 1.42 – 1.26 (m, 4 H, 3-H, 4-H), 1.31 – 1.10 (m, 2 H, 5-H), 0.86 (d, J = 6.5 Hz, 6 H, 7-H, 8-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 63.2 (t, C-1), 39.1 (t, C-5), 33.0 (t, C-2), 28.1 (d, C-6), 27.3, 26.1 (2t, C-3, C-4), 22.8 (q, C-7, C-8) ppm.

IR (ATR): ν_{max} = 3325, 2952, 2927, 2867, 1465, 1052 cm^{-1}.

6-Methylheptanoic acid (63)

exp: 41
DL304



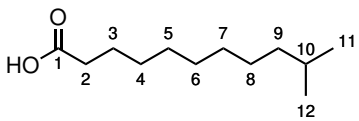
According to GP 2, the reaction of alcohol **62** (3.00 g, 23.0 mmol) with $KMnO_4$ (29.1 g, 184 mmol) and NaOH (11.1 g, 276 mmol) yielded **63** as a yellow oil (3.53 g, quant.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.73 (br. s, 1 H, $CO_2\underline{H}$), 2.34 (t, J = 7.5 Hz, 2 H, 2-H), 1.66 – 1.39 (m, 3 H, 3-H, 6-H), 1.66 – 1.39 (m, 2 H, 4-H) 1.22 – 1.10 (m, 2 H, 5-H), 0.85 (d, J = 6.6 Hz, 6 H, 7-H, 8-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 180.7 (s, C-1), 38.6 (t, C-5), 34.3 (t, C-2), 27.9 (d, C-6), 27.0, 25.0 (2t, C-3 to C-4), 22.7 (q, C-7, C-8) ppm.

10-Methylundecanoic acid (64)

exp: 42
DL494



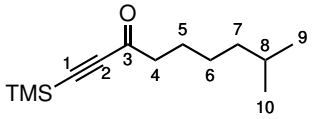
According to GP 2, the reaction of 10-methylundecanol (15 g, 80.5 mmol) with $KMnO_4$ (38.2 g, 241 mmol) and NaOH (14.5 g, 362 mmol) yielded **64** as a colorless wax (13.1 g, 81 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.70 (br. s, 1 H, $CO_2\underline{H}$), 2.34 (t, J = 7.5 Hz, 2 H, 2-H), 1.72 – 1.54 (m, 2 H, 3-H), 1.59 – 1.41 (m, 1 H, 10-H), 1.40 – 1.21 (m, 1 H, 4-H to 8-H), 1.20 – 1.10 (m, 2 H, 9-H), 0.86 (d, J = 6.6 Hz, 6 H, 11-H, 12-H) ppm.

The analytical data is consistent with literature reports.[76]

8-Methyl-1-(trimethylsilyl)non-1-yn-3-one (65)

exp: 43
DL307

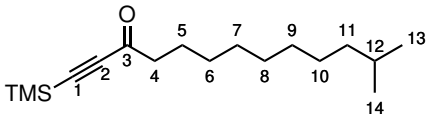


According to GP 11, the reaction of carboxylic acid **63** (1.00 g, 6.93 mmol) with $SOCl_2$ (18.9 mL, 260 mmol), $AlCl_3$ (5.45 g, 40.8 mmol) and BTMSA (7.59 g, 44.6 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 20/1, eluting at 20/1), **65** as a brown liquid (953 mg, contains 45 % desilylated product, 72 % combined yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.56 (t, J = 7.3 Hz, 2 H, 4-H), 1.64 (pd, J = 6.8, 6.3, 4.6 Hz, 2 H, 5-H), 1.58 – 1.42 (m, 1 H, 8-H), 1.38 – 1.23 (m, 2 H, 6-H), 1.16 (dt, J = 8.7, 6.6 Hz, 2 H, 7-H), 0.85 (d, J = 6.6 Hz, 6 H, 9-H, 10-H), 0.23 (s, 9 H, $Si(C\underline{H_3})_3$) ppm.

12-Methyl-1-(trimethylsilyl)tridec-1-yn-3-one (66)

exp: 44
DL274



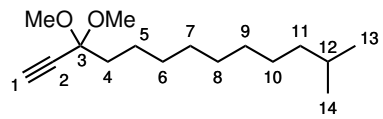
According to GP 11, the reaction of 10-methylundecanoic acid (6.00 g, 14.0 mmol) with $SOCl_2$ (15.2 mL, 210 mmol), $AlCl_3$ (4.39 g, 33.0 mmol) and BTMSA (6.12 g, 35.9 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/1→7/1), **66** as a brown liquid (6.58 g, 78 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.52 (t, J = 7.4 Hz, 2 H, 4-H), 1.63 (p, J = 7.3 Hz, 2 H, 5-H), 1.49 (hept, J = 6.6 Hz, 1 H, 12-H), 1.38 – 1.16 (m, 12 H, 6-H to 10-H), 1.16 – 0.95 (m, 1 H, 11-H), 0.83 (d, J = 6.7 Hz, 5 H, 13-H, 14-H), 0.21 (s, 8 H, $Si(C\underline{H_3})_3$) ppm.

IR (ATR): ν_{max} = 2955, 2925, 2855, 1679, 1251, 1095, 842 cm^{-1}.

3,3-Dimethoxy-12-methyltridec-1-yne (67)

exp: 45
DL413



Trimethyl orthoacetate (16.0 mL, 140 mmol), MeOH (30 mL) and toluenesulfonic acid (480 mg, 2.52 mmol) were added to a solution of alkynone **66** (10.0 g, 35.7 mmol) in CH_2Cl_2 (35.7 mL) and the mixture was stirred at r.t. for 2 h. After addition of KOH (5.70 g, 100 mmol), the reaction was stirred at r.t. for 2 h. Then H_2O was added, the aqueous phase extracted with TBME, the combined organic phase was washed with brine and dried over $MgSO_4$. The extract filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 100/1 → 20/1, eluting at 20/1) to yield **67** as a yellowish oil (6.68 g, 74 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.29 (s, 6 H, OC$\underline{H_3}$), 2.52 (s, 1 H, 1-H), 1.83 – 1.71 (m, 2 H, 4-H), 1.57 – 1.38 (m, 3 H, 5-H to 10-H, 12-H), 1.37 – 1.17 (m, 10 H, 5-H to 10-H), 1.17 – 1.03 (m, 2 H, 11-H), 0.85 (d, J = 6.6 Hz, 6 H, 13-H, 14-H) ppm.

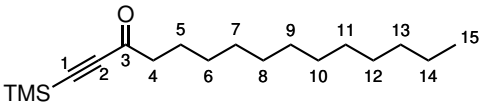
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 99.3 (s, C-3), 80.6 (s, C-2), 73.4 (d, C-1), 50.0 (q, O$\underline{C}H_3$), 39.2 (t, C-11), 37.2 (t, C-4), 30.0, 29.7, 29.64, 29.62 (4t, C-5 to C-10), 28.1 (d, C-12), 27.5, 24.1 (2t, C-5 to C-10), 22.8 (q, C-13, C-14) ppm.

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{16}H_{31}O_2$ 255.2319, found 255.2319.

IR (ATR): ν_{max} = 2952, 2924, 2853, 1464, 1137, 1047 cm^{-1}.

1-(Trimethylsilyl)pentadec-1-yn-3-one (69)

exp: 46
DL599



According to GP 11, the reaction of tridecanoic acid (3.00 g, 14.0 mmol) with $SOCl_2$ (4.47 mL, 61.6 mmol), $AlCl_3$ (2.80 g, 21.0 mmol) and BTMSA (2.62 g, 15.4 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/1→10/1), **69** as a brown liquid (3.92 g, 95 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.52 (t, J = 7.4 Hz, 2 H, 4-H), 1.64 (p, J = 7.2 Hz, 3 H, 5-H), 1.43 – 1.13 (m, 18 H, 6-H to 14-H), 0.94 – 0.75 (m, 3 H, 15-H), 0.22 (s, 9 H, Si(C$\underline{H_3}$)$_3$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 188.1 (s, C-3), 102.2 (s, C-2), 97.5 (s, C-1), 45.4 (t, C-4), 32.0, 29.8, 29.7, 29.7, 29.5, 29.5, 29.4, 29.0 (8 t, C-6 to C-14), 24.0 (t, C-5), 22.8 (t, C-6 to C-14), 14.2 (q, C-15), −0.7 (q, Si($\underline{C}H_3$)$_3$) ppm.

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{18}H_{35}OSi$ 295.2452, found 295.2441.

IR (ATR): ν_{max} = 2954, 2924, 2854, 2170, 1249 cm^{-1}.

The analytical data is consistent with literature reports.[178]

Triisopropyl((trimethylsilyl)ethynyl)silane (70)

exp: 47
DL162

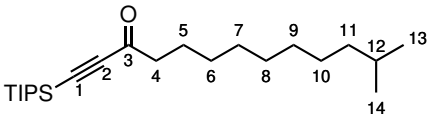
A solution of *n*-BuLi (1.98 mL, 2.50 M in hexanes, 4.94 mmol) was added dropwise to a solution of ethynyltrimethylsilane (485 mg, 4.94 mmol) in THF (7.50 mL) at −78 °C. The mixture was stirred at −78 °C for 10 min, warmed to 0 °C and allowed to proceed for 20 min. After cooling to −78 °C, TIPSCl was added dropwise, the reaction stirred at −78 °C for 15 min and warmed to r.t. over 16 h. NH_4Cl solution was added, the aqueous phase was extracted with EtOAc, the combined organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield **70** as a colorless liquid (1.14 g, 91 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.12 – 0.98 (m, 23 H, SiCH(C$\underline{H_3}$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.17 (s, 9 H, Si(C$\underline{H_3}$)$_3$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 116.3, 110.3 (2s, C-1, C-2), 18.7 (q, SiCH($\underline{C}H_3$)$_2$), 11.2 (d, Si$\underline{C}$H(CH$_3$)$_2$), 0.2 (q, Si($\underline{C}H_3$)$_3$) ppm.

12-Methyl-1-(triisopropylsilyl)tridec-1-yn-3-one (71)

exp: 48
DL201



According to GP 11, reaction of 10-methylundecanoic acid **64** (100 mg, 499 µmol) with $SOCl_2$ (253 µL, 3.49 mmol), $AlCl_3$ (73.2 mg, 549 µmol) and triisopropyl((trimethylsilyl)ethynyl)silane **70** (152 mg, 599 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 20/1) **71** as a brownish oil (167 mg, 92 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.56 (t, J = 7.4 Hz, 2 H, 4-H), 1.71 (p, J = 7.2 Hz, 2 H, 5-H), 1.58 – 1.45 (m, 1 H, 12-H), 1.40 – 1.22 (m, 14 H, 6-H to 10-H), 1.22 – 0.97 (m, 33 H, 11-H, SiCH($C\underline{H}_3$)$_2$, SiC$\underline{H}$(CH_3)$_2$), 0.87 (d, J = 6.5 Hz, 6 H, 13-H, 14-H) ppm.

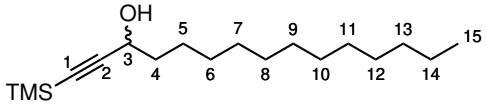
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 188.3 (s, C-3), 104.3, 95.5 (2s, C-1, C-2), 45.8 (t, C-4), 39.2 (t, C-11), 30.0, 29.6, 29.5, 29.1 (4t, C-5 to C-10), 28.1 (d, C-12), 27.5, 24.4 (2t, C-5 to C-10), 22.8 (q, C-13, C-14), 18.6 (q, SiCH($\underline{C}H_3$)$_2$), 11.1 (d, Si$\underline{C}$H(CH_3)$_2$) ppm.

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{23}H_{45}OSi$ 365.3234, found 365.3230.

IR (ATR): ν_{max} = 2924, 2865, 2145, 1679, 1462 cm^{-1}.

1-(Trimethylsilyl)pentadec-1-yn-3-ol (72)

exp: 49
DL499



$NaBH_4$ (19.3 mg, 509 µmol) was added to a solution of alkynone **69** (200 mg, 679 µmol) in EtOH (969 µL) and the reaction stirred at r.t. for 1 h. HCl solution (1 M) was added carefully until gas development ceased. The aqueous phase was extracted with CH_2Cl_2, the combined organic phase washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 100/0 →0/100, eluting at 88/12) to yield **72** as a colorless oil (55.9 mg, 28 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.34 (t, J = 6.6 Hz, 2 H, 3-H), 1.79 – 1.56 (m, 2 H, 4-H), 1.53 – 1.37 (m, 2 H, 5-H to 14-H), 1.35 – 1.20 (m, 18 H, 5-H to 14-H), 0.87 (t, J = 6.9 Hz, 3 H, 15-H), 0.16 (s, 9 H, Si($C\underline{H}_3$)$_3$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 107.2 (s, C-2), 89.4 (s, C-1), 63.1 (d, C-3), 37.9 (t, C-4), 32.1, 29.83, 29.79, 29.69, 29.65, 29.5, 29.4, 25.3, 22.8 (9 t, C-5 to C-14), 14.2 (q, C-15), 0.0 (q, Si($\underline{C}H_3$)$_3$) ppm.

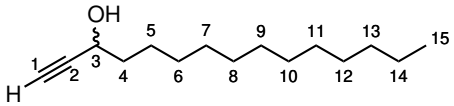
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{18}H_{36}NaOSi$ 319.2428, found 319.2421.

IR (ATR): ν_{max} = 2922, 2853, 1248, 1013 cm^{-1}.

$[\alpha]_D^{25}$**:** -1.86° (c = 1.0; $CHCl_3$).

Pentadec-1-yn-3-ol (73)

exp: 50
DL499



73, a side product in the synthesis of **72**, was isolated as a colorless solid (79.6 mg, 52 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.36 (td, J = 6.6, 2.1 Hz, 1 H, 3-H), 2.45 (d, J = 2.1 Hz, 1 H, 1-H), 1.91 (br. s, 1 H, O-H), 1.77 – 1.63 (m, 2 H, 4-H), 1.50 – 1.38 (m, 2 H, 5-H to 14-H), 1.37 – 1.18 (m, 18 H, 5-H to 14-H), 0.88 (t, J = 6.9 Hz, 3 H, 15-H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 85.2 (s, C-2), 72.9 (s, C-1), 62.5 (d, C-3), 37.8 (t, C-4), 32.1, 29.81, 29.78, 29.70, 29.66, 29.5, 29.4, 25.2, 22.8 (9 t,C-5 to C-14), 14.2 (C-15) ppm.

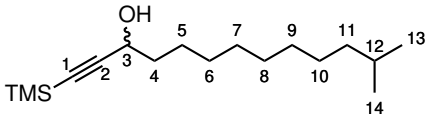
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{15}H_{26}NaO$ 319.2433, found 319.2421.

IR (ATR): ν_{max} = 3376, 3285, 2919, 2851, 1470, 1066 cm^{-1}.

$[\alpha]_D^{25}$**:** +2.36° (c = 1.0; $CHCl_3$).

12-Methyl-1-(trimethylsilyl)-tridec-1-yn-3-ol (74)

exp: 51
DL495



$NaBH_4$ (19.3 mg, 509 µmol) was added to a solution of alkynone **66** (200 mg, 713 µmol) in EtOH and the reaction stirred at r.t. for 3 h. HCl solution (1 M) was added carefully until gas formation ceased. The aqueous phase was extracted with CH_2Cl_2, the combined organic phase was washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 100/0 →0/100, eluting at 88/12) to yield **74** as a colorless oil (116 mg, 58 %).

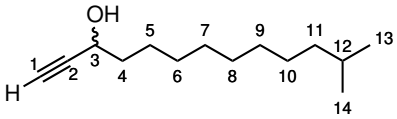
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.37 (t, J = 6.6 Hz, 1 H, 3-H), 1.88 – 1.58 (m, 2 H, 4-H), 1.60 – 1.06 (m, 15 H, 5-H to 12-H), 0.88 (d, J = 6.6 Hz, 6 H, 13-H, 14-H), 0.17 (s, 8 H, $Si(C\underline{H_3})_3$) ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{17}H_{34}NaOSi$ 305.2271, found 305.2265.

IR (ATR): ν_{max} = 2954, 2924, 2854, 2170, 1249 cm^{-1}.

12-Methyltridec-1-yn-3-ol (75)

exp: 52
DL495



75, a side product in the synthesis of **74**, was isolated as a colorless oil (18.1 mg, 12 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.36 (td, J = 6.6, 2.1 Hz, 1 H, 3-H), 2.45 (d, J = 2.1 Hz, 1 H, 1-H), 1.77 – 1.62 (m, 2 H, 4-H), 1.59 – 1.38 (m, 3 H, 5-H to 10-H, 12-H), 1.38 – 1.18 (m, 8 H, 5-H to 10-H) 1.18 – 1.01 (m, 2 H, 11-H) 0.86 (d, J = 6.9 Hz, 6 H, 13-H, 14-H) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 85.2 (s, C-2), 72.9 (s, C-1), 62.5 (d, C-3), 39.2 (t, C-11) 37.7 (t, C-4), 30.0, 29.72, 29.65, 29.4 (4 t, C-5 to C-10), 28.1 (d, C-12), 27.5, 25.2 (2 t,C-5 to C-10), 22.8 (q, C-13, C-14) ppm.

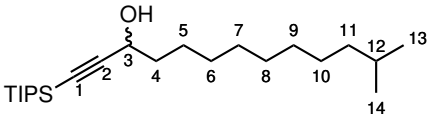
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{14}H_{26}NaOSi$ 233.1876, found 233.1868.

IR (ATR): ν_{max} = 2951, 2924, 2854, 2092, 1465 cm^{-1}.

$[\alpha]_D^{25}$**:** +3.44° (c = 1.0; $CHCl_3$).

12-Methyl-1-(triisopropylsilyl)tridec-1-yn-3-ol (76)

exp: 53
DL202

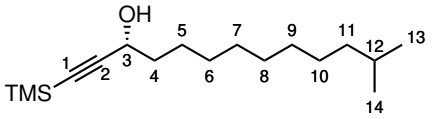


Alkynone **71** (50.0 mg, 137 µmol) was added to a solution of $NaBH_4$ (3.11 mg, 82.3 µmol) in EtOH (200 µL) and the reaction stirred at r.t. for 4 h. NH_4Cl solution (1 M) was added until gas development ceased. The aqueous phase was extracted with EtOAc, the combined organic phase washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 10/1) to yield **74** as a colorless oil (27.0 mg, 54 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.38 (t, J = 6.6 Hz, 1 H, 3-H), 1.78 – 1.63, 1.56 – 1.43 (2m, 2x 3 H, 4-H, 12-H, $SiCH(C\underline{H}_3)_2$), 1.37 – 1.22 (m, 10 H, 5-H10), 1.20 – 1.03 (m, 24 H, 11-H, $SiCH(C\underline{H}_3)_2$), 0.86 (d, J = 6.5 Hz, 6 H, 13-H, 14-H) ppm.

(*R*)-12-Methyl-1-(trimethylsilyl)-tridec-1-yn-3-ol (77)

exp: 54
DL491



According to GP 12, the reaction of 12-methyl-1-(trimethylsilyl)tridec-1-yn-3-one (2.00 g, 7.13 mmol) with RuCl[(*R*,*R*)-TsDPEN](mesitylene) (90.7 mg, 143 µmol), Et_3N (5.93 mL, 42.8 mmol) and formic acid (1.34 mL, 35.7 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0→7/1), **77** as a brownish oil (1.40 g, 69 %).

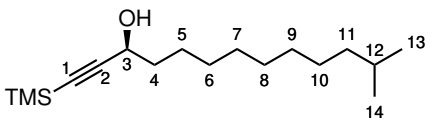
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.37 (t, J = 6.6 Hz, 1 H, 3-H), 1.88 – 1.58 (m, 2 H, 4-H), 1.60 – 1.06 (m, 15 H, 5-H to 12-H), 0.88 (d, J = 6.6 Hz, 6 H, 13-H, 14-H), 0.17 (s, 8 H, $Si(C\underline{H}_3)_3$) ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{17}H_{34}NaOSi$ 305.2271, found 305.2265.

IR (ATR): ν_{max} = 2954, 2924, 2854, 2170, 1249 cm^{-1}.

(*S*)-12-Methyl-1-(trimethylsilyl)-tridec-1-yn-3-ol (78)

exp: 55
DL483



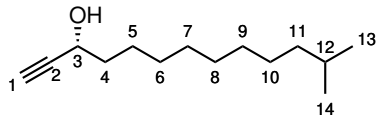
According to GP 12, reaction of alkynone **66** (500 mg, 1.78 mmol) with RuCl[(*S*,*S*)-TsDPEN](mesitylene) (22.7 mg, 35.7 µmol), Et_3N (1.48 mL, 10.7 mmol) and formic acid (336 µL, 8.91 mmol) yielded, after flash

chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 88/12), **78** as a yellowish oil (266 mg, 52 %).

$[\alpha]_D^{25}$**:** -0.52° ($c = 1.0$; $CHCl_3$).

(*R*)-12-Methyl-1-tridec-1-yn-3-ol (SI-13)

exp: 56
DL500



According to GP 13, the reaction of (*R*)-1-(trimethylsilyl)pentadec-1-yn-3-ol (1.50 g, 5.31 mmol) with KOH (1.19 g, 21.2 mmol) yielded **SI-13** as a yellow oil (1.12 g, quant.).

^{1}**H-NMR (**500 MHz**, $CDCl_3$):** δ = 4.36 (td, J = 6.6, 2.1 Hz, 1 H, 3-H), 2.45 (d, J = 2.1 Hz, 1 H, 1-H), 1.77 – 1.62 (m, 2 H, 4-H), 1.59 – 1.38 (m, 3 H, 5-H to 10-H, 12-H), 1.38 – 1.18 (m, 8 H, 5-H to 10-H) 1.18 – 1.01 (m, 2 H, 11-H) 0.86 (d, J = 6.9 Hz, 6 H, 13-H, 14-H) ppm.

^{13}**C-NMR (**151 MHz**, $CDCl_3$):** δ = 85.2 (s, C-2), 72.9 (s, C-1), 62.5 (d, C-3), 39.2 (t, C-11) 37.7 (t, C-4), 30.0, 29.72, 29.65, 29.4 (4 t, C-5 to C-10), 28.1 (d, C-12), 27.5, 25.2 (2 t,C-5 to C-10), 22.8 (q, C-13, C-14) ppm.

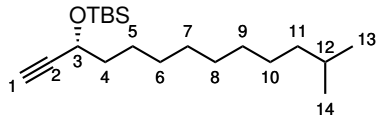
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{14}H_{26}NaOSi$ 233.1876, found 233.1868.

IR (ATR): ν_{max} = 2951, 2924, 2854, 2092, 1465 cm^{-1}.

$[\alpha]_D^{25}$**:** +3.44° ($c = 1.0$; $CHCl_3$).

(*R*)-*tert*-Butyldimethyl((12-methyl-1-tridec-1-yn-3-yl)oxy)silane (79)

exp: 57
DL503



According to GP 14, the reaction of (*R*)-12-methyl-1-tridec-1-yn-3-ol (600 mg, 2.85 mmol) with DIPEA (845 µL, 4.85 mmol), 4-DMAP (34.9 mg, 285 µmol) and TBSCl (623 mg, 4.14 mmol) yielded **79** as a yellowish liquid (943 mg, quant.).

^{1}**H-NMR (**600 MHz**, $CDCl_3$):** δ = 4.33 (td, J = 6.5, 2.1 Hz, 1 H, 3-H), 2.36 (d, J = 2.1 Hz, 1 H, 1-H), 1.76 – 1.61 (m, 2 H, 4-H), 1.51 (hept, J = 6.6 Hz, 1 H, 12-H), 1.46 – 1.36 (m, 2 H, 5-H to 10-H), 1.33 – 1.20 (m, 10 H, 5-H to 10-H), 1.15 (q, J = 6.8 Hz, 2 H, 11-H), 0.91 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.86 (d, J = 6.7 Hz, 6 H, 13-H, 14-H), 0.13, 0.11 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}**C-NMR (**151 MHz**, $CDCl_3$):** δ = 86.0 (s, C-2), 72.0 (d, C-1), 62.9 (d, C-3), 39.2 (t, C-11), 38.7 (t, C-4), 30.1, 29.8, 29.7, 29.4, 28.1, 27.6 (5t, C-5 to C-10), 25.9 (q, $SiC(\underline{C}H_3)_3$), 25.3 (d, C-12), 22.8 (q, C-13, C-14), 18.4 (s, $Si\underline{C}(CH_3)_3$), −4.4, −4.9 (2q, $Si(\underline{C}H_3)_2$) ppm.

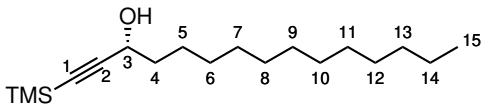
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{20}H_{40}NaOSi$ 347.2741, found 347.2744.

IR (ATR): ν_{max} = 2928, 2856, 1643, 1537, 1460, 1250, 1126 cm^{-1}.

$[\alpha]_D^{25}$**:** +32.5° ($c = 1.0$; $CHCl_3$).

(*R*)-1-(Trimethylsilyl)pentadec-1-yn-3-ol (80)

exp: 58
DL498



According to GP 12, the reaction of 1-(trimethylsilyl)pentadec-1-yn-3-one (2.0 g, 6.79 mmol) with RuCl-[(*R*,*R*)-TsDPEN](mesitylene) (130 mg, 203 µmol), Et_3N (5.65 mL, 40.7 mmol) and formic acid (1.28 mL, 34.0 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0→7/1), **80** as a brown oil (1.72 g, 86 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.34 (t, J = 6.6 Hz, 2 H, 3-H), 1.79 – 1.56 (m, 2 H, 4-H), 1.53 – 1.37 (m, 2 H, 5-H to 14-H), 1.35 – 1.20 (m, 18 H, 5-H to 14-H), 0.87 (t, J = 6.9 Hz, 3 H, 15-H), 0.16 (s, 9 H, $Si(C\underline{H}_3)_3$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 107.2 (s, C-2), 89.4 (s, C-1), 63.1 (d, C-3), 37.9 (t, C-4), 32.1, 29.83, 29.79, 29.69, 29.65, 29.5, 29.4, 25.3, 22.8 (9 t, C-5 to C-14), 14.2 (q, C-15), 0.0 (q, $Si(\underline{C}H_3)_3$) ppm.

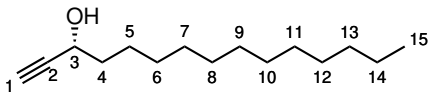
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{18}H_{36}NaOSi$ 319.2428, found 319.2421.

IR (ATR): ν_{max} = 2922, 2853, 1248, 1013 cm^{-1}.

$[\alpha]_D^{25}$**:** -1.86° (c = 1.0; $CHCl_3$).

(*R*)-Pentadec-1-yn-3-ol (SI-14)

exp: 59
DL501



According to GP 13, the reaction of alcohol **80** (1.10 g, 3.71 mmol) with KOH (832 mg, 14.8 mmol) yielded **SI-14** as a yellow wax (882 mg, quant.).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.36 (td, J = 6.6, 2.1 Hz, 1 H, 3-H), 2.45 (d, J = 2.1 Hz, 1 H, 1-H), 1.91 (br. s, 1 H, O-H), 1.77 – 1.63 (m, 2 H, 4-H), 1.50 – 1.38 (m, 2 H, 5-H to 14-H), 1.37 – 1.18 (m, 18 H, 5-H to 14-H), 0.88 (t, J = 6.9 Hz, 3 H, 15-H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 85.2 (s, C-2), 72.9 (s, C-1), 62.5 (d, C-3), 37.8 (t, C-4), 32.1, 29.81, 29.78, 29.70, 29.66, 29.5, 29.4, 25.2, 22.8 (9 t,C-5 to C-14), 14.2 (C-15) ppm.

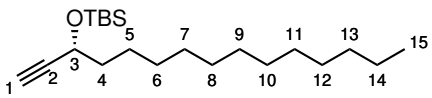
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{15}H_{26}NaO$ 319.2433, found 319.2421.

IR (ATR): ν_{max} = 3376, 3285, 2919, 2851, 1470, 1066 cm^{-1}.

$[\alpha]_D^{25}$**:** +2.36° (c = 1.0; $CHCl_3$).

(*R*)-*tert*-Butyldimethyl(pentadec-1-yn-3-yloxy)silane (81)

exp: 60
DL504



According to GP 14, the reaction of (*R*)-pentadec-1-yn-3-ol (700 mg, 3.12 mmol) with DIPEA (923 µL, 5.30 mmol), 4-DMAP (38.1 mg, 312 µmol and TBSCl (658 mg, 4.37 mmol)) yielded **81** as a yellowish liquid (1.05 g, quant.).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.33 (td, J = 6.5, 2.1 Hz, 1 H, 3-H), 2.36 (d, J = 2.1 Hz, 1 H, 1-H), 1.78 – 1.55 (m, 2 H, 4-H), 1.50 – 1.35 (m, 2 H, 5-H to 14-H), 1.36 – 1.18 (m, 18 H, 5-H to 14-H), 0.91 (s, 9 H, SiC($\underline{CH_3}$)$_3$), 0.88 (t, J = 6.9 Hz, 3 H, 15-H), 0.14, 0.11 (2s, 2x 3 H, Si($\underline{CH_3}$)$_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 86.0 (s, C-2), 72.0 (d, C-1), 63.0 (d, C-3), 38.8 (t, C-4), 32.1, 29.9, 29.82, 29.76, 29.72, 29.5, 29.4 (7 t, C-5 to C-14),26.0 (q, SiC($\underline{C}H_3$)$_3$), 25.3, 22.9 (2 t, C-5 to C-14), 18.4 (s, Si$\underline{C}$(CH$_3$)$_3$), 14.3 (q, C-15), −4.4, −4.9 (2 t, Si($\underline{C}H_3$)$_2$) ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{21}H_{42}NaOSI$ 361.2897, found 361.2906.

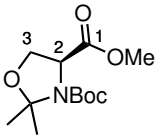
IR (ATR): ν_{max} = 2952, 2924, 2854, 1463, 1250 cm^{-1}.

$[\alpha]_D^{25}$**:** +28.2° (c = 1.0; $CHCl_3$).

4.4.2 Hydrometallation approach for the synthesis of (*3S*)-isomers

3-(*tert*-Butyl) 4-methyl (*S*)-2,2-dimethyloxazolidine-3,4-dicarboxylate (84)

exp: 61
DL611



Toluenesulfonic acid (2.17 g, 11.4 mmol) in toluene (10 mL) and 2,2-dimethoxypropane (125 mL, 1.03 mol) were added to a solution of *N*-Boc-L-serine methyl ester (50.0 g, 228 mmol) in toluene (456 mL). The mixture was refluxed using a Dean-Stark apparatus for 24 h, the solvent reduced *in vacuo* and the remains mixed with sat. $NaHCO_3$ solution (60 mL) and extracted with TBME (3x). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and vacuum-distilled to yield **84** as a yellowish liquid (28.7 g, 48 %).

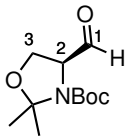
b.p. = 87 °C (0.9 hPa)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.46 (dd, J = 6.7, 2.7 Hz, 1 H, 2-H)*, 4.35 (dd, J = 7.0, 3.1 Hz, 1 H, 2-H), 4.12 (dt, J = 9.2, 6.6 Hz, 1 H, 3-H), 4.01 (ddd, J = 9.3, 7.1, 2.9 Hz, 1 H, 3-H), 3.73 (s, 3 H, OC$\underline{H_3}$), 1.65 (s, 2 H), 1.61 (s, 1 H), 1.51 (s, 2 H, each C(C$\underline{H_3}$)$_2$), 1.47 (s, 5 H), 1.39 (s, 5 H, Boc−C(C$\underline{H_3}$)$_3$) ppm.
*minor rotamer

The analytical data is consistent with literature reports.[107]

Garner's aldehyde (11)

exp: 62
DL618



A pre-cooled solution of DIBAL-H (120 mL, 1.2 M in toluene) was added over 100 min to a solution of **84** (28.7 g, 110 mmol) in CH_2Cl_2 (1000 mL) at −78 °C. The reaction was stirred at −78 °C for 4 h.

After complete consumption of the starting material, MeOH (5 mL) was added slowly at −78 °C and the internal temperature was kept below −75 °C. The mixture was warmed to r.t., poured into saturated Na/K-tartrate solution and stirred until phase separation became visible (2 h). The aqueous phase was extracted with CH_2Cl_2, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude distilled under reduced pressure to yield **11** as a colorless oil (18.2 g, 71 %).

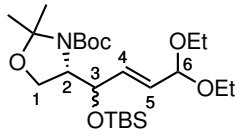
b.p. = 56 °C, (<0.1 hPa)

^{1}H-NMR (300 MHz**, $CDCl_3$):** δ = 9.54 (dd, J = 16.8, 2.2 Hz, 1 H, 1-H), 4.31 (dt, J = 5.6, 2.5 Hz, 1 H, 2-H)*, 4.16 (dt, J = 6.4, 3.2 Hz, 1 H, 2-H), 4.12 – 3.98 (m, 2 H, 3-H), 1.61 (s, 2 H), 1.56 (s, 1 H)*, 1.52 (s, 2 H, each C($C\underline{H}_3$)$_2$), 1.48 (s, 4 H), 1.40 (s, 6 H, each Boc−C($C\underline{H}_3$)$_3$) ppm. *minor rotamer

The analytical data is consistent with literature reports.[107]

tert-Butyl (*S*)-4-((*E*)-1-((*tert*-butyldimethylsilyl)oxy)-4,4-diethoxybut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (85)

exp: 63
DL374/
DL380



According to GP 17, the reaction of 3,3-diethoxy-1-propyne (486 mg, 3.79 mmol) with Schwartz' reagent (1.03 g, 3.99 mmol), Et_2Zn (4.73 mL, 4.25 mmol) and Garner's aldehyde **11** (750 mg, 3.27 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 4/1 → 2/1), as a yellowish oil, which was used directly in the next step.

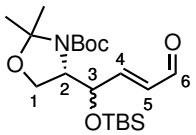
According to GP 15, the reaction of alcohol **SI-15** with 2,6-lutidine (338 µL, 2.92 mmol), 4-DMAP (15.3 mg, 125 µmol) and TBSOTf (384 µL, 1.67 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 80/20), **85** as a yellowish oil (254 mg, 31 % over two steps; 55/45 diastereomeric mixture).

^{1}H-NMR (300 MHz**, $CDCl_3$):** δ = 6.00 – 5.82 (m, 1 H, 4-H), 5.75 – 5.58 (m, 1 H, 5-H), 4.92 (d, J = 4.5 Hz, 1 H, 6-H), 4.72 (t, J = 5.4 Hz, 1 H, 3-H), 4.65 – 4.51 (m, 1 H, 3-H), 4.12 – 3.91 (m, 1 H, 1-H), 3.91 – 3.80 (m, 2 H, 1-H, 2-H), 3.70 (q, J = 7.0 Hz, 2 H, OC$\underline{H}_2$CH$_3$), 3.53 – 3.39 (m, 2 H, OC$\underline{H}_2$CH$_3$), 1.54, 1.48 (2s, 2x 3 H, C($C\underline{H}_3$)$_2$), 1.47 (s, 9 H, Boc−C($C\underline{H}_3$)$_3$), 1.43, 1.40 (2s, 2x 3 H, C($C\underline{H}_3$)$_2$), 1.18, 1.17 (2t, J = 7.1 Hz, 2x 3 H, OCH$_2$C$\underline{H}_3$), 0.87 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.08, 0.03 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (75 MHz**, $CDCl_3$):** δ = 152.7, 152.2 (2s, Boc−CO), 132.9, 132.5 (2d, C-4), 129.4, 129.2 (2d, C-5), 101.0, 100.7 (2d, C-6), 95.0, 94.3 (2s, $\underline{C}$(CH$_3$)$_2$), 80.2, 80.1 (2s, Boc−$\underline{C}$(CH$_3$)$_3$), 70.9, 70.2 (2d, C-3), 63.1, 62.9 (2t, C-1), 60.9, 60.8, 60.7, 60.5 (4t, OCH$_2$CH$_3$), 58.5 (d, C-2), 28.8, 28.5 (2q, Boc−C($\underline{C}$H$_3$)$_3$), 26.4, 25.9, 24.5, 23.1 (4q, SiC($\underline{C}$H$_3$)$_3$, C($\underline{C}$H$_3$)$_2$), 18.2 (s, Si$\underline{C}$(CH$_3$)$_3$), 15.4 (q, OCH$_2\underline{C}$H$_3$), −4.4, −4.7 (2q, Si($\underline{C}$H$_3$)$_2$) ppm.

tert-Butyl (*4S*)-4-((*E*)-1-((*tert*-butyldimethylsilyl)oxy)-4-oxobut-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (86)

exp: 64
DL390



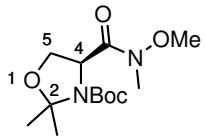
H_2O (15.2 µL, 844 µmol) and PPTS (10.6 mg, 42.2 µmol) were added to a solution of acetal **85** (200 mg, 422 µmol) in CH_2Cl_2 (8.44 mL) and the reaction was stirred at r.t. for 3 h. $MgSO_4$ was added, the suspension was filtered and the volatiles removed *in vacuo* to yield **86** as a yellow oil (112 mg, 66 %, 55/45 mixture of diastereomers).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.59 (d, J = 8.0 Hz, 1 H, 6-H), 6.89 (dd, J = 15.5, 4.6 Hz, 1 H, 4-H), 6.29 (dd, J = 15.6, 8.0 Hz, 1 H, 5-H), 4.94 (t, J = 4.9 Hz, 1 H, 3-H), 4.82 (d, J = 5.0 Hz, 1 H, 3-H), 4.13 – 3.83 (m, 3 H, 1-H, 2-H), 1.55 (s, 3 H, C($C\underline{H_3}$)$_2$), 1.49 (s, 9 H, Boc–C($C\underline{H_3}$)$_3$), 1.44, 1.43, 1.42 (3s, 3x 3 H, C($C\underline{H_3}$)$_2$), 0.89 (s, 9 H, SiC($C\underline{H_3}$)$_3$), 0.13, 0.09 (2s, 2x 3 H, Si($C\underline{H_3}$)$_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 193.6, 193.4 (2s, C-6), 156.5, 155.7 (2s, Boc–CO), 132.5, 132.4 (2d, C-4), 127.1, 126.2 (2d, C-5), 95.2, 94.6 (2s, $\underline{C}(CH_3)_2$), 80.8 (s, Boc–$\underline{C}(CH_3)_3$), 70.6, 70.0 (2s, C-3), 63.0, 62.8 (2t, C-1), 53.6 (d, C-2), 28.8, 28.5 (2q, Boc–C($\underline{C}H_3$)$_3$), 26.8, 25.8, 24.1, 22.7 (4q, SiC($\underline{C}H_3$)$_3$, C($\underline{C}H_3$)$_2$), 18.1 (s, Si$\underline{C}$(CH$_3$)$_3$), −4.7, −4.6 (2q, Si($\underline{C}H_3$)$_2$) ppm.

tert-Butyl (*S*)-4-(methoxy(methyl)carbamoyl)-2,2-dimethyloxazolidine-3-carboxylate (89)

exp: 65
DL169



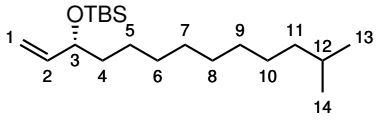
N,*O*-Dimethylhydroxylamine hydrochloride (1.69 g, 17.4 mmol) was added to a solution of methyl ester **84** (3.00 g, 11.6 mmol) in THF (23.4 mL) and the slurry cooled to −20 °C. Isopropylmagnesium bromide (9.64 mL, 3.00 M, 28.9 mmol) was added dropwise and the reaction stirred below −10 °C for 1 h. NH_4Cl solution was added and the aqueous phase extracted with EtOAc, the combined organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield **89** as a yellow wax(3.21 g, 96 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.79 (dd, J = 7.2, 2.9 Hz), 4.71 (dd, J = 7.4, 3.6 Hz, together 1 H, 4-H), 4.18 (dt, J = 9.2, 7.5 Hz, 1 H, 5-H), 3.94 (ddd, J = 20.9, 9.2, 3.3 Hz, 1 H, 5-H), 3.74, 3.69 (2s, 3 H, O$C\underline{H_3}$), 3.20 (s, 3 H, N$C\underline{H_3}$), 1.69, 1.67 (2s, together 3 H, C($C\underline{H_3}$)$_2$), 1.56, 1.51 (2s, together 3 H, C($C\underline{H_3}$)$_2$), 1.49, 1.40 (2s, together 9 H, Boc–C($C\underline{H_3}$)$_3$) ppm.

The analytical data is consistent with literature reports.[179]

(*R*)-*tert*-Butyldimethyl((12-methyltridec-1-en-3-yl)oxy)silane (91)

exp: 66
DL128



According to GP 16, the reaction of alkynol **79** (380 mg, 1.17 mmol) with Schwartz' reagent (408 mg, 1.58 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 6/1 → 4/1, eluting at 6/1), **91** as a yellowish oil (196 mg, quant.).

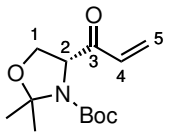
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.79 (ddd, J = 16.7, 10.3, 6.0 Hz, 1 H, 2-H), 5.12 (dt, J = 17.2, 1.6 Hz, 1 H, 1-H), 5.00 (dt, J = 10.3, 1.5 Hz, 1 H, 1-H), 4.14 – 3.96 (m, 1 H, 3-H), 1.54 – 1.37 (m, 4 H, 4-H to 12-H), 1.39 – 1.13 (m, 14 H, 4-H to 12-H), 1.20 – 0.97 (m, 2 H, 4-H to 12-H), 0.89 (s, 9 H, SiC(C$\underline{H_3}$)$_3$), 0.86 (d, J = 6.7 Hz, 6 H, 13-H, 14-H), 0.05, 0.03 (2s, 2x 3 H, Si(C$\underline{H_3}$)$_2$) ppm.

IR (ATR): ν_{max} = 2949, 2923, 2852, 1645, 1457, 1250, 1027 cm^{-1}.

$[\alpha]_D^{25}$**:** -0.37° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-acryloyl-2,2-dimethyloxazolidine-3-carboxylate (92)

exp: 67
DL113

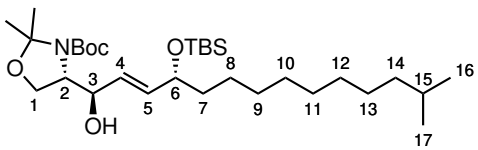


A solution of vinylmagnesium bromide (1.04 mL, 1.04 mmol) was added to a solution of Weinreb amide **89** (200 mg, 694 µmol) in THF (4.62 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and at r.t. for 48 h. HCl (1 M) was added, the mixture extracted with EtOAc, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude purified by flash chromatography (cyclohexane/EtOAc 90/10 → 84/16, eluting at 84/16) to yield **92** as a yellowish oil (36.3 mg, 21 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.57 (ddd, J = 17.7, 14.8, 10.5 Hz, 1 H, 4-H), 6.42 – 6.28 (m, 1 H, 5-H), 5.85 (dd, J = 10.5, 1.5 Hz, 1 H, 5-H), 4.74 (dd, J = 7.3, 3.2 Hz), 4.56 (dd, J = 7.6, 3.7 Hz, together 1 H, 2-H), 4.25 – 4.11 (m, 1 H, 1-H), 3.94 (ddd, J = 16.4, 9.2, 3.5 Hz, 1 H, 1-H), 1.70, 1.64 (2s, together 5 H, C(C$\underline{H_3}$)$_2$), 1.55, 1.52, 1.49, 1.36 (4s, together 13 H, C(C$\underline{H_3}$)$_2$, Boc–C(C$\underline{H_3}$)$_3$) ppm.

tert-Butyl (*S*)-4-((*1R,4R,E*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (93)

exp: 68
DL555



A solution of Red-Al® in toluene (63 µL, 3.6 M, 158 µmol) was added dropwise to a solution of alkyne **100** (50.0 mg, 90.3 µmol) in THF (1.81 mL) at −10 °C leading to observable gas development. The reaction was warmed to 0 °C over 90 min and saturated Na/K-tartrate solution was added. The aqueous phase was extracted with TBME (3x), the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield **93** as a colorless oil (49.9 mg, 70 % over two steps).

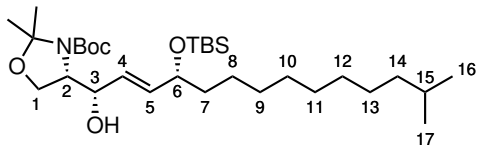
^{1}H-NMR (500 MHz, C_6D_6): δ = 5.91 (dd, J = 15.4, 5.9 Hz, 1 H, 5-H), 5.74 (dd, J = 15.5, 5.2 Hz, 1 H, 4-H), 4.49 – 4.39 (m, 1 H, 3-H), 4.28 – 4.15 (m, 1 H, 6-H), 4.12 – 3.92 (m, 1 H, 2-H), 3.72 – 3.67 (m, 2 H,

1-H), 1.86 – 1.22 (m, 30 H, C($C\underline{H}_3$)$_2$, Boc–C($C\underline{H}_3$)$_3$, 7-H to 14-H), 1.22 – 1.10 (m, 2 H, 7-H to 15-H), 1.02 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.90 (d, J = 6.5 Hz, 6 H, 16-H, 17-H), 0.12 (s, 6 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (126 MHz, C_6D_6): δ = 136.1 (d, C-5), 129.0 (d, C-4), 94.8 (s, $\underline{C}(CH_3)_2$), 80.4 (s, Boc–$\underline{C}(CH_3)_3$) 73.4 (d, C-6), 73.3 (d, C-3), 64.7 (t, C-1), 39.9 (t, C-14), 33.0 (t, C-7), 30.23, 30.21, 30.1, 29.8 (4t, C-8 to C-13), 28.5 (q, Boc–C($\underline{C}H_3$)$_3$), 26.3 (t, C-8 to C-13), 26.1 (d, C-15), 25.6 (q, C($\underline{C}H_3$)$_2$, SiC($\underline{C}H_3$)$_3$), 22.9 (q, C-16, C-17), 18.5 (s, Si$\underline{C}$(CH$_3$)$_3$), −3.9, −4.4 (2q, Si($\underline{C}H_3$)$_2$) ppm.

tert-Butyl (*S*)-4-((*1S,4R,E*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (94)

exp: 69
DL561



According to GP 17, the reaction of alkynol **79** (96.6 mg, 298 µmol) with Schwartz' reagent (80.4 mg, 312 µmol), Et_2Zn (378 µL, 340 µmol) and Garner's aldehyde **11** (65.0 mg, 284 µmol) yielded, after flash chromatography (cyclohexane/EtOAc100/0 → 50/50, eluting at 80/20), **94** as a yellow oil (78.7 mg, 50 %).

^{1}H-NMR (500 MHz, C_6D_6): δ = 5.83 (dd, J = 15.4, 5.9 Hz, 1 H, 5-H), 5.73 (dd, J = 15.4, 5.7 Hz, 2 H, 4-H), 4.53 – 4.30 (m, 1 H, 3-H), 4.25 – 4.10 (m, 1 H, 6-H), 4.08 – 3.93 (m, 1 H, 2-H), 3.93 – 3.83 (m, 1 H, 1-H), 3.74 – 3.60 (m, 1 H, 1-H), 1.70 – 1.57 (m, 4 H, 7-H to 14-H), 1.57 – 1.23 (m, 28 H, C($C\underline{H}_3$)$_2$, Boc–C($C\underline{H}_3$)$_3$, 7-H to 15-H), 1.01 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.90 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.12 (s, 6 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (126 MHz, C_6D_6): δ = 136.8 (d, C-5), 129.0 (d, C-4), 94.8 (s, $\underline{C}(CH_3)_2$), 80.5 (s, Boc–$\underline{C}(CH_3)_3$), 73.4 (d, C-6), 73.2 (d, C-3), 64.6 (t, C-1), 62.7 (d, C-2), 39.9 (t, C-14), 33.0 (t, C-7), 30.23, 30.21, 30.1, 29.8 (4t, C-8 to C-13), 28.4 (q, Boc–C($\underline{C}H_3$)$_3$), 26.3 (t, C-8 to C-13), 26.1 (d, C-15), 25.6 (q, C($\underline{C}H_3$)$_2$, SiC($\underline{C}H_3$)$_3$), 22.9 (q, C-16, C-17), 18.5 (s, Si$\underline{C}$(CH$_3$)$_3$), −3.8, −4.4 (2q, Si($\underline{C}H_3$)$_2$) ppm.

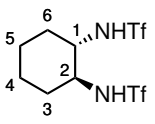
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{31}H_{61}NNaO_5Si$ 578.4211, found 578.4223.

IR (ATR): ν_{max} = 2926, 2854, 1698, 1375, 1364, 1251 cm^{-1}.

$[\alpha]_D^{25}$**:** -28.6° (c = 1.1; $CHCl_3$).

N,N′-((*1S,2S*)-Cyclohexane-1,2-diyl)bis(1,1,1-trifluoromethanesulfonamide) (95)

exp: 70
EK001



DIPEA (3.55 mL, 24.1 mmol) was added to a solution of (*1S,2S*)-1,2-diaminocyclohexane (600 mg, 5.26 mmol) in CH_2Cl_2 (16 mL) and the solution stirred at 0 °C for 30 min. After cooling to −40 °C, trifluoromethanesulfonylchloride (1.18 mL, 10.5 mmol) was added dropwise to the solution and the cooling bath was removed after complete addition. The mixture was stirred at r.t. for 30 min and aqueous HCl solution (30 mL, 1 M) was added, the aqueous phase extracted with TBME, the combined organic phase washed with brine and dried over Na_2SO_4. The extract was filtered, the volatiles removed *in vacuo* and the crude

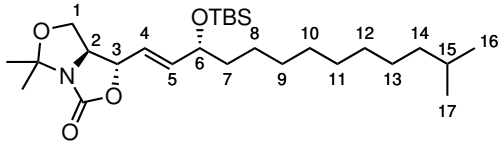
product purified by flash chromatography (cyclohexane/EtOAc 100/0 → 80/20). The obtained solid was recrystallized from refluxing CH_2Cl_2 to yield **95** as a colorless solid (690 mg, 37 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.24 (d, J = 7.6 Hz, 2 H, N-H), 3.31 – 3.13 (m, 2 H, 1-H, 2-H), 2.29 – 2.13 (m, 2 H, 3-H, 6-H), 1.94 – 1.74 (m, 2 H, 3-H, 6-H), 1.51 – 1.14 (m, 4 H, 4-H, 5-H) ppm.

The analytical data is consistent with literature reports.[116]

(*1S,7aS*)-1-((*R,E*)-3-((*tert*-Butyldimethylsilyl)oxy)-12-methyltridec-1-en-1-yl)-5,5-dimethyldihydro-1*H*,3*H*,5*H*-oxazolo[3,4-c]oxazol-3-one (96)

exp: 71
DL270



NaH (10.8 mg, 60 % in paraffin, 269 µmol) was added to a solution of oxazolidine **94** (100 mg, 180 µmol) in DMF (1.8 mL) at 0 °C and the reaction was stirred at 100 °C for 16 h. Further NaH (10.8 mg, 269 µmol) was added at r.t and the mixture stirred at 100 °C for 6 h. After cooling to r.t., Na_2CO_3 solution was added, the aqueous phase was extracted with EtOAc, the combined organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles were removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtoAc 10/1) to yield **96** as a colorless oil (10.0 mg, 11 %, 2/1 diastereomeric mixture in the 3-position).

Major isomer:

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.85 (ddt, J = 15.4, 5.5, 1.1 Hz, 1 H, 5-H), 5.72 (ddt, J = 15.4, 7.2, 1.5 Hz, 1 H, 4-H), 4.72 – 4.65 (m, 1 H, 3-H), 4.19 – 4.09 (m, 2 H, 1-H, 6-H), 4.10 – 4.01 (m, 1 H, 2-H), 3.68 (ddt, J = 8.7, 7.7, 3.1 Hz, 1 H, 1-H), 1.73 (s, 3 H, C($C\underline{H}_3$)$_2$), 1.55 – 1.46 (m, 3 H, 7-H, 15-H), 1.44 (s, 3 H, C($C\underline{H}_3$)$_2$), 1.36 – 1.20 (m, 18 H, 8-H to 13-H), 1.18 – 1.10 (m, 2 H, 14-H), 0.89 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.04, 0.02 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 156.9 (s, CO), 139.6 (d, C-5), 125.0 (d, C-4), 95.1 (s, $\underline{C}(CH_3)_2$), 79.0 (d, C-3), 72.1, (d, C-6), 67.9 (t, C-1), 64.4 (d, C-2), 39.2 (t, C-14), 38.1 (t, C-7), 30.0, 29.9, 29.8, 29.7 (4t, C-8 to C-13), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 26.0 (q, SiC($\underline{C}H_3$)$_3$, C($\underline{C}H_3$)$_2$), 25.2 (q, C($\underline{C}H_3$)$_2$), 23.5 (t, C-8 to C-13), 22.8 (q, C-16, C-17), 18.4 (s, Si$\underline{C}$(CH$_3$)$_3$), −4.2, −4.6 (2q, Si($\underline{C}H_3$)$_2$) ppm.
Minor isomer:

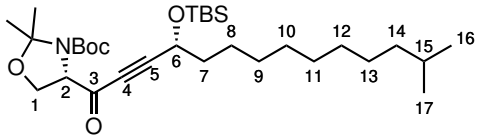
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.94 – 5.89 (m, 1 H, 5-H), 5.58 (ddd, J = 15.3, 6.6, 1.5 Hz, 1 H, 4-H), 5.12 – 5.05 (m, 1 H, 3-H), 4.43 – 4.36 (m, 1 H, 2-H), 4.19 – 4.09 (m, 1 H, 6-H), 3.86 (dd, J = 8.6, 6.3 Hz, 1 H, 1-H), 3.68 (ddt, J = 8.7, 7.7, 3.1 Hz, 1 H, 1-H), 1.71 (s, 3 H, AcetonidMeH), 1.55 – 1.46 (m, 3 H, 7-H, 15-H), 1.45 (s, 3 H, C($C\underline{H}_3$)$_2$), 1.36 – 1.20 (m, 18 H, 8-H to 13-H), 1.18 – 1.10 (m, 2 H, 14-H), 0.89 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.07, 0.02 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 156.9 (s, CO), 139.7 (d, C-5), 121.3 (d, C-4), 95.2 (s, $\underline{C}(CH_3)_2$), 74.7 (d, C-3), 71.9, (d, C-6), 64.4 (t, C-1), 61.8 (d, C-2), 39.2 (t, C-14), 38.0 (t, C-7), 30.0, 29.9, 29.8, 29.7 (4t, C-8 to C-13), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 26.0 (q, SiC($\underline{C}H_3$)$_3$, C($\underline{C}H_3$)$_2$), 25.2 (q, C($\underline{C}H_3$)$_2$), 23.5 (t, C-8 to C-13), 22.8 (q, C-16, C-17), 18.4 (s, Si$\underline{C}$(CH$_3$)$_3$), −4.2, −4.6 (2q, Si($\underline{C}H_3$)$_2$) ppm.

4.4.3 Alkynilation of serine derivatives

tert-Butyl 4-(4-((*tert*-butyldimethylsilyl)oxy)-13-methyltetradec-2-ynoyl)-2,2-dimethyloxazolidine-3-carboxylate (97)

exp: 72
DL158



n-BuLi (1.26 mL, 2.5 M in hexanes, 3.16 mmol) was added to a solution of alkyne **79** (945 mg, 2.91 mmol) in THF (5.83 mL) at −10 °C and the reaction stirred for 2 h. The mixture was cooled to −78 °C, a solution of Weinreb amide **89** (700 mg, 2.43 mmol) in THF (4.86 mL) was added dropwise and the reaction was slowly warmed to r.t. over 16 h. NH_4Cl solution was added, the aqueous phase extracted with EtOAc, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 20/1 → 10/1, eluting at 10/1) to yield **97** as a yellowish oil (910 mg, 68 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.53 – 4.44 (m, 1 H, 6-H), 4.41 (dt, J = 7.1, 3.5 Hz, 1 H, 2-H), 4.23 – 4.02 (m, 2 H, 1-H), 1.78 – 1.61 (m, 4 H, 7-H), 1.54, 1.50 (2s, 2x 3 H, C($C\underline{H}_3$)$_2$), 1.42 (s, 9 H, Boc−C($C\underline{H}_3$)$_3$), 1.34 – 1.21 (m, 18 H, 8-H to 13-H), 1.21 – 1.08 (m, 2 H, 14-H), 0.90 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.13, 0.10 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 185.1 (s, C-3), 151.3 (s, Boc−CO), 97.0 (s, C-5)95.6 (s, $\underline{C}(CH_3)_2$), 81.1 (s, C-4), 80.9 (s, Boc−$\underline{C}(CH_3)_3$), 66.9 (d, C-2), 65.5 (t, C-1), 62.9 (d, C-6), 39.2 (t, C-14), 38.0 (t, C-7), 30.0, 29.7, 29.6, 29.3 (4t, C-8 to C-13), 28.4 (q, Boc−C($\underline{C}H_3$)$_3$), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 25.8 (q, SiC($\underline{C}H_3$)$_3$), 25.4, 24.4 (2q, C($\underline{C}H_3$)$_2$), 22.8 (q, C-16, C-17), 18.3 (s, Si$\underline{C}$(CH$_3$)$_3$), −4.4, −4.9 (2q, Si($\underline{C}H_3$)$_2$) ppm.

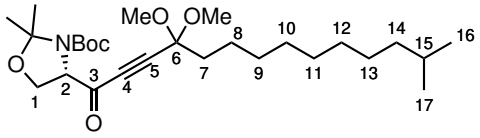
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{31}H_{58}NO_5Si$ 552.4079, found 552.4067.

IR (ATR): ν_{max} = 2926, 2855, 2207, 1715, 1463, 1365, 1257, 1170, 1093 cm^{-1}.

$[\alpha]_D^{25}$**:** -16.1° (c = 1.0; $CHCl_3$).

tert-Butyl (*R*)-4-(4,4-dimethoxy-13-methyltetradec-2-ynoyl)-2,2-dimethyloxazolidine-3-carboxylate (98)

exp: 73
DL414



n-BuLi (3.60 mL, 2.40 M, 8.65 mmol) was added to a solution of alkyne **67** (2.00 g, 7.86 mmol) in THF (15.7 mL) at −10 °C and the reaction stirred at −10 °C for 30 min. The mixture was cooled to −78 °C, a solution of Weinreb amide **89** (2.49 g, 8.65 mmol) in THF (17.3 mL) was added dropwise and the reaction stirred at −78 °C for 16 h. $NaHCO_3$ solution was added, the aqueous phase extracted with TBME, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 100/0 → 50/50, eluting at 90/10) to yield **98** as a colorless oil (279 mg, 7 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.56 (t, J = 4.7 Hz, 1 H, 2-H)*, 4.44 – 4.38 (m, J = 7.2, 3.5 Hz, 1 H, 2-H), 4.20 – 4.10 (m, 1 H, 1-H), 4.07 (dd, J = 9.4, 3.3 Hz, 1 H, 1-H), 3.29 (s, 6 H, $OC\underline{H}_3$), 1.84 – 1.73 (m, 2 H, 7-H), 1.69 (s, 2 H), 1.63 (s, 1 H, $C(C\underline{H}_3)_2$)*, 1.55 – 1.33 (m, 15 H), 1.33 – 1.17 (m, 11 H, 8-H to 13-H, 15-H, $C(C\underline{H}_3)_2$, Boc–$C(C\underline{H}_3)_3$), 1.17 – 1.08 (m, 2 H, 14-H), 0.84 (d, J = 6.6 Hz, 6 H, 16-H, 17-H) ppm.
*minor rotamer

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 185.1 (s, C-3), 184.4 (s, C-3)*, 152.4 (s, Boc–CO), 151.3 (s, Boc–CO)*, 99.7 (s, C-6), 95.7 (s, $\underline{C}(CH_3)_2$), 94.9 (s, $\underline{C}(CH_3)_2$)*, 90.7 (s, C-5), 90.6 (s, C-5)*, 81.3 (s, Boc–$\underline{C}(CH_3)_3$)*, 81.2 (s, C-4)*, 81.1 (s, Boc–$\underline{C}(CH_3)_3$), 80.8 (s, C-4), 66.9 (d, C-2)*, 66.8 (d, C-2), 65.5 (t, C-1), 65.1 (t, C-1)*, 50.5 (q, $O\underline{C}H_3$)*, 50.3 (q, $O\underline{C}H_3$), 39.1 (t, C-14), 36.91 (t, C-7)*, 36.86 (t, C-7), 30.0, 29.7, 29.6, 28.5, 28.3 (5t, C-8 to C-13), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 25.3 (q, $C(\underline{C}H_3)_2$), 25.1 (q, $C(\underline{C}H_3)_2$)*, 24.3 (q, Boc–$C(\underline{C}H_3)_3$), 24.0 (C-8 to C-13), 23.9 (q, Boc–$C(\underline{C}H_3)_3$)*, 22.8 (q, C-16, C-17), ppm.
*minor rotamer

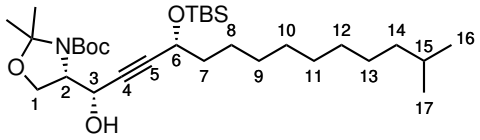
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{27}H_{47}NNaO_6$ 504.3296, found 504.3285.

IR (ATR): ν_{max} = 2926, 2855, 2216, 1713, 1697, 1456, 1365, 1266, 1167 cm^{-1}.

$[\alpha]_D^{25}$: -32.2° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*1S,4R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (99)

exp: 74
DL165



DIBAL-H (308 µL, 1.20 M in toluene, 370 µmol) was added to a solution of alkynone **97** (170 mg, 308 µmol) in THF (6.00 mL) at −10 °C and the reaction stirred at −10 °C for 2 h. H_2O was added, the aqueous phase extracted with EtOAc, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield **99** as a yellowish oil (79.3 mg, 46 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.81 – 4.41 (m, 1 H, 2-H), 4.39 – 4.29 (m, 1 H, 6-H), 4.19 – 3.84 (m, 3 H, 1-H, 3-H), 1.76 – 1.56 (m, 5 H, 7-H, $C(C\underline{H}_3)_2$), 1.50 (s, 12 H, $C(C\underline{H}_3)_2$, Boc–$C(C\underline{H}_3)_3$), 1.44 – 1.34 (m, 2 H, 8-H to 13-H, 15-H), 1.32 – 1.19 (m, 10 H, 8-H to 13-H), 1.19 – 1.07 (m, 2 H, 14-H), 0.89 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.86 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.11, 0.09 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.1 (s, Boc–CO), 95.1 (s, $\underline{C}(CH_3)_2$), 88.1 (s, C-5), 81.9 (s, C-4), 81.5 (s, Boc–$\underline{C}(CH_3)_3$), 66.8 (d, C-2), 65.6 (t, C-1), 63.1 (d, C-6), 62.6 (d, C-3), 39.2 (t, C-14), 38.7 (t, C-7), 30.0, 29.8, 29.7, 29.4 (4t, C-8 to C-13), 28.5 (q, Boc–$C(\underline{C}H_3)_3$), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 25.9 (q, $SiC(\underline{C}H_3)_3$, $C(\underline{C}H_3)_2$), 25.4 (q ,$C(\underline{C}H_3)_2$), 22.8 (q, C-16, C-17), 18.3 (s, $Si\underline{C}(CH_3)_3$), −4.3, −4.9 (2q, $Si(\underline{C}H_3)_2$) ppm.

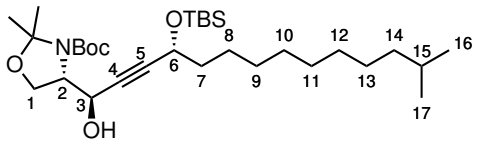
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{31}H_{60}NO_5Si$ 554.4235, found 554.4227.

IR (ATR): ν_{max} = 2951, 2926, 2855, 1695, 1463, 1391, 1365, 1251, 1170, 1070 cm^{-1}.

$[\alpha]_D^{25}$: -16.2° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*1R,4R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (100)

exp: 75
DL553



A solution of *n*-BuLi in hexanes (308 µL, 2.20 M, 678 µmol) was added dropwise to a solution of silyl ether **79** (200 mg, 616 µmol) in THF (1.23 mL) at −78 °C and the mixture stirred for 30 min. Solutions of HMPA (441 mg, 2.46 mmol) in THF (1.23 mL) and Garner's aldehyde **11** (169 mg, 739 µmol) in THF (1.48 mL) were added slowly at −78 °C subsequently. After stirring for 45 min at −78 °C, the cooling bath was removed and the reaction stirred for further 3 h at r.t. Sat. NH_4Cl solution was added, the aqueous phase extracted with CH_2Cl_2, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified *via* flash chromatography (cyclohexane/EtOAc 100/0 → 50/50, eluting at 85/15) to yield **100** as a yellowish oil (242 mg, 70 %).

^{1}H-NMR (500 MHz, C_6D_6): δ = 4.97 – 4.54 (m, 2 H, 3-H), 4.45 (t, J = 6.3 Hz, 1 H, 6-H), 4.15 – 3.93 (m, 1 H, 1-H), 3.88 – 3.63 (m, 2 H, 1-H, 2-H), 1.82 – 1.67 (m, 5 H, 7-H, $C(C\underline{H_3})_2$), 1.59 – 1.07 (m, 34 H, 8-H to 15-H, Boc−$C(C\underline{H_3})_3$, $C(C\underline{H_3})_2$), 1.00 (s, 9 H, $SiC(C\underline{H_3})_3$), 0.90 (d, J = 6.5 Hz, 6 H, 16-H, 17-H), 0.23, 0.16 (2s, 2x 3 H, $Si(C\underline{H_3})_2$) ppm.

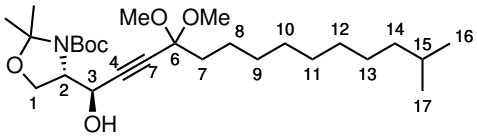
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{31}H_{60}NO_5Si$ 554.4235, found 554.4222.

IR (ATR): ν_{max} = 2955, 2927, 2856, 1697, 1456, 1388, 1365, 1250, 1170, 1085 cm^{-1}.

$[\alpha]_D^{25}$**:** -2.39° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*R*)-1-hydroxy-4,4-dimethoxy-13-methyltetradec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (101)

exp: 76
DL465



According to GP 12, the reaction of alkynone **98** (500 mg, 1.04 mmol) with RuCl[(*S,S*)-TsDPEN](mesitylene) (33.0 mg, 51.9 µmol), Et_3N (863 µL, 6.23 mmol) and formic acid (196 µL, 5.19 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 80/20, eluting at 85/15), **101** as a yellowish oil (410 mg, 82 %).

Alternatively, the reaction of alkyne **67** (14.7 g, 57.6 mmol) with *n*-BuLi (32.7 mL, 72.0 mmol), DMPU (52.2 mL, 432 mmol) and Garner's aldehyde **11** (10.0 g, 48.0 mmol) according to GP 18 yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 80/20, eluting at 85/15), **101** as yellowish oil (15.0 g, 65 %). exp:77 PRM010

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.89 – 4.79 (m, 1 H, 3-H)*, 4.65 – 4.51 (m, 1 H, 3-H)*, 4.29 – 3.83 (m, 3 H, 1-H, 2-H), 3.23 (s, 6 H, $OC\underline{H_3}$), 1.78 – 1.67 (m, 2 H, 7-H), 1.64 – 1.55 (m, 3 H, 8-H to 13-H, 15-H), 1.55 – 1.37 (m, 16 H, 8-H to 13-H, $C(C\underline{H_3})_2$, Boc−$C(C\underline{H_3})_3$), 1.34 – 1.17 (m, 13 H, 8-H to 13-H), 1.15 – 1.03 (m, 2 H, 14-H), 0.81 (d, J = 6.6 Hz, 6 H, 16-H, 17-H) ppm. *Rotamer peaks

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.1 (s, Boc–CO), 99.4 (s, C-6), 95.1 (s, $\underline{C}(CH_3)_2$), 83.5 (s, C-4), 82.6 (s, C-5), 81.4 (s, Boc–$\underline{C}(CH_3)_3$), 65.0 (t, C-1), 63.7 (d, C-3), 62.4 (d, C-2), 50.0 (q, O$\underline{C}H_3$), 39.1 (t, C-14), 37.2 (t, C-7), 29.9, 29.7, 29.6, 29.6 (4t, C-8 to C-13), 28.4 (q, Boc–C($\underline{C}H_3)_3$), 28.0 (d, C-15), 27.4 (t, C-8 to C-13), 25.9, 25.2 (2q, C($\underline{C}H_3)_2$), 22.7 (q, C-16, C-17), ppm.

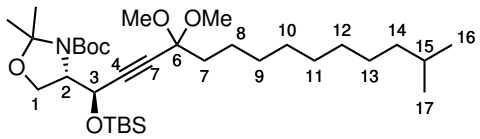
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{27}H_{49}NNaO_6$ 506.3452, found 506.3442.

IR (ATR): ν_{max} = 3445, 2926, 2854, 1695, 1669, 1456, 1390, 1365, 1260, 1169, 1050 cm^{-1}.

$[\alpha]_D^{25}$**:** -35.5° (c = 3.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-4,4-dimethoxy-13-methyltetradec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (104)

exp: 78
DL624



According to GP 14, the reaction of alkynol **101** (300 mg, 620 µmol) with DIPEA (186 µL, 1.05 mmol), 4-DMAP (7.58 mg, 62.0 µmol and TBSCl (131 mg, 868 µmol)) yielded, after flash chromatography (cyclohexane/EtOAc 97/3 → 50/50, eluting at 90/10), **104** as a yellowish oil (325 mg, 87 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.16 – 5.11 (m, 1 H, 3-H), 4.30 – 4.18 (m, 1 H, 1-H), 4.18 – 3.91 (m, 2 H, 1-H, 2-H), 3.24 (s, 6 H, O$\underline{C}H_3$), 1.57 – 1.35 (m, 21 H, 7-H to 13-H, 15-H, C($\underline{C}H_3)_2$, Boc–C($\underline{C}H_3)_3$), 1.34 – 1.18 (m, 13 H, 7-H to 13-H), 1.18 – 1.07 (m, 2 H, 14-H), 0.89 (s, 9 H, SiC($\underline{C}H_3)_3$), 0.84 (d, J = 6.7 Hz, 6 H, 16-H, 17-H) 0.11, 0.05 (2s, 2x 3 H, Si($\underline{C}H_3)_2$) ppm.

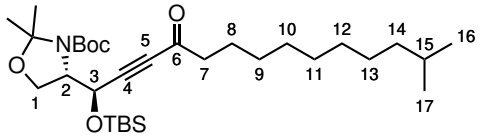
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 152.6 (s, Boc–CO), 99.6 (s, C-6), 94.7 (s, $\underline{C}(CH_3)_2$), 84.9 (s, C-4), 82.3 (s, C-5), 80.4 (s, Boc–$\underline{C}(CH_3)_3$), 63.6 (t, C-1), 62.2 (d, C-2), 60.4 (d, C-3), 50.3 (q, O$\underline{C}H_3$), 39.2 (t, C-14), 37.6 (t, C-7), 30.0, 29.8, 29.75, 29.70 (4t, C-8 to C-13), 28.6 (q, Boc–C($\underline{C}H_3)_3$), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 26.2, 26.0 (2q, C($\underline{C}H_3)_2$), 22.8 (q, C-16, C-17), 18.3 (s, Si$\underline{C}(CH_3)_3$) −4.7, −4.9 (2q, Si($\underline{C}H_3)_2$) ppm.

IR (ATR): ν_{max} = 2953, 2927, 2856, 1706, 1690, 1457, 13 900, 1364, 1258, 1170 cm^{-1}.

$[\alpha]_D^{25}$**:** +50.5° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-13-methyl-4-oxotetradec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (105)

exp: 79
DL628



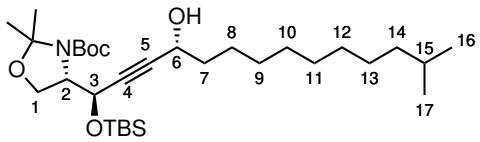
A solution of alkyne **104** (230 mg, 385 mmol) and toluenesulfonic acid (7.32 mg, 38.5 µmol) in acetone (3.85 mL) was stirred at r.t. for 3 h. Na_2CO_3 solution was added, the mixture extracted with CH_2Cl_2, the combined organic phase was washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield **105** as a yellowish oil (208 mg, 98 %).

^{1}H-NMR (300 MHz, **$CDCl_3$**): δ = 5.16 – 5.11 (m, 1 H, 3-H), 4.19 – 4.08 (m, 1 H, 1-H), 4.08 – 3.93 (m, 2 H, 1-H, 2-H), 2.62 – 2.38 (m, 2 H, 7-H), 1.75 – 1.36 (m, 22 H, 8-H to 13-H, 15-H, C($C\underline{H_3}$)$_2$, Boc–C($C\underline{H_3}$)$_3$), 1.36 – 1.06 (m, 12 H, 8-H to 13-H), 1.17 – 1.05 (m, 2 H, 14-H), 0.90 (s, 9 H, SiC($C\underline{H_3}$)$_3$), 0.84 (d, J = 6.5 Hz, 6 H, 16-H, 17-H), 0.14, 0.08 (2s, 2x 3 H, Si($C\underline{H_3}$)$_2$) ppm.

^{13}C-NMR (75 MHz, **$CDCl_3$**): δ = 187.5 (s, C-6), 152.6 (s, Boc–CO), 94.6 (s, $\underline{C}(CH_3)_2$), 90.7 (s, C-4), 84.2 (s, C-5) 80.6 (s, Boc–$\underline{C}(CH_3)_3$), 63.7 (t, C-1), 61.7 (d, C-2), 61.1 (d, C-3), 45.6 (t, C-7), 39.1 (t, C-14), 29.9, 29.62, 29.57, 29.53, 29.4, 29.1 (6t, C-8 to C-13), 28.5 (q, Boc–C($\underline{C}H_3$)$_3$), 28.1 (d, C-15), 27.5, 27.0 (2t, C-8 to C-13), 25.9, 25.5 (2q, C($\underline{C}H_3$)$_2$), 22.8 (q, C-16, C-17), 18.3 (s, Si$\underline{C}$(CH$_3$)$_3$), −4.7, −4.8 (2q, Si($\underline{C}H_3$)$_2$) ppm.

tert-Butyl (*S*)-4-((*1R*,*4R*)-1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-13-methyltetradec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (106)

exp: 80
DL631



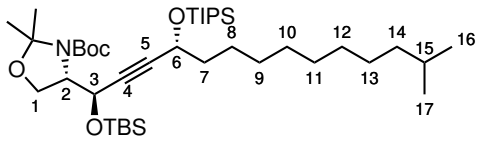
According to GP 12, the reaction of alkynone **105** (100 mg, 181 µmol) with RuCl[(*R*,*R*)-TsDPEN](mesitylene) (5.76 mg, 9.06 µmol), Et_3N (151 µL, 1.09 mmol) and formic acid (34.2 µL, 906 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 80/20), **106** as a reddish oil (37.2 mg, 37 %).

^{1}H-NMR (500 MHz, **$CDCl_3$**): δ = 5.03 – 4.85 (m, 1 H, 3-H), 4.45 – 4.29 (m, 1 H, 6-H), 4.24 – 4.08 (m, 1 H, 1-H), 4.10 – 3.92 (m, 2 H, 1-H, 2-H), 1.79 – 1.58 (m, 2 H, 7-H to 13-H), 1.58 – 1.45 (m, 15 H, 7-H to 13-H, 15-H, C($C\underline{H_3}$)$_2$, Boc–C($C\underline{H_3}$)$_3$), 1.45 – 1.34 (m, 2 H, 7-H to 13-H), 1.34 – 1.17 (m, 12 H, 7-H to 13-H), 1.17 – 1.08 (m, 2 H, 14-H), 0.90 (s, 9 H, SiC($C\underline{H_3}$)$_3$), 0.85 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.12, 0.08 (2s, 2x 3 H, Si($C\underline{H_3}$)$_2$) ppm.

^{13}C-NMR (126 MHz, **$CDCl_3$**): δ = 152.8 (s, Boc–CO), 94.6 (s, $\underline{C}(CH_3)_2$), 86.6 (s, C-5), 84.6 (s, C-4), 80.5 (s, Boc–$\underline{C}(CH_3)_3$), 63.9 (t, C-1), 62.5 (d, C-6), 62.2 (d, C-2), 61.1 (d, C-3), 39.2 (t, C-14), 37.9 (t, C-7), 30.0, 29.8, 29.7, 29.4 (t, C-8 to C-13), 28.6 (q, SiC($\underline{C}H_3$)$_3$), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 26.0, 25.6 (2q, C($\underline{C}H_3$)$_2$), 22.8 (q, C-16, C-17), 18.3 (s, SiC($\underline{C}H_3$)$_3$) 4.6 (q, Si($\underline{C}H_3$)$_2$) ppm.

tert-Butyl (*S*)-4-((*5R*,*8R*)-10,10-diisopropyl-2,2,3,3,11-pentamethyl-8-(9-methyldecyl)-4,9-dioxa-3,10-disiladodec-6-yn-5-yl)-2,2-dimethyloxazolidine-3-carboxylate (107)

exp: 81
PRM017



2,6-Lutidine (310 µL, 2.67 mmol), 4-DMAP (16.3 mg, 134 µmol) and TIPSOTf (467 µL, 1.74 mmol) were added to a solution of alkyne **108** (740 mg, 1.34 mmol) in CH_2Cl_2 (13.4 mL) at 0 °C and the mixture stirred at r.t. for 16 h. Citric acid solution (10 wt − % in H_2O) was added and the aqueous phase extracted with TBME. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, the volatiles

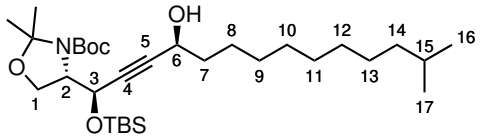
removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 85/15) to yield **107** as a colorless oil (838 mg, 88 %).

^{1}H-NMR (300 MHz**, C_6D_6):** δ = 5.53 – 5.44, 5.19 – 5.10 (2m, together 1 H, 3-H), 4.57 (t, J = 6.0 Hz, 1 H), 4.52 – 4.45 (m, 1 H, 2-H, 6-H), 4.33 – 3.97 (m, 2 H, 1-H), 1.89 – 1.74 (m, 2 H, 7-H to 13-H, 15-H, C(C$\underline{H}_3$)$_2$, Boc–C(C$\underline{H}_3$)$_3$), 1.72 – 1.55 (m, 2 H, 7-H to 13-H, 15-H, C(C$\underline{H}_3$)$_2$, Boc–C(C$\underline{H}_3$)$_3$), 1.55 – 1.38 (m, 7 H, 7-H to 13-H, 15-H, C(C$\underline{H}_3$)$_2$, Boc–C(C$\underline{H}_3$)$_3$), 1.37 – 1.26 (m, 4 H, 7-H to 13-H), 1.24 – 1.10 (m, 24 H, 14-H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 1.05 (s, 9 H, SiC(C$\underline{H}_3$)$_3$), 0.95 – 0.82 (m, 6 H, 16-H, 17-H), 0.28, 0.21 (2s, 2x 3 H, Si(C$\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (75 MHz**, C_6D_6):** δ = 152.6 (s, Boc–CO), 94.8 (s, $\underline{C}$(CH$_3$)$_2$), 87.8 (s, C-5), 84.1 (s, C-4), 79.7 (s, Boc–$\underline{C}$(CH$_3$)$_3$), 64.1 (t, C-1), 63.7, 63.0 (2d, C-3, C-6), 61.3 (d, C-2), 39.9 (t, C-14), 39.5 (t, C-7), 30.5, 30.4, 30.2, 30.10, 30.07, 29.94, 29.90 (7t, C-8 to C-13), 28.6 (q, Boc–C($\underline{C}$H$_3$)$_3$), 26.3 (q, Si($\underline{C}$H$_3$)$_2$), 25.4 (t, C-8 to C-13), 22.9 (q, C-16, C-17), 18.6 (s, Si$\underline{C}$(CH$_3$)$_3$), 18.4 (q, SiCH($\underline{C}$H$_3$)$_2$), 12.8 (d, Si$\underline{C}$H(CH$_3$)$_2$), −4.3, −4.5 (2q, Si($\underline{C}$H$_3$)$_2$) ppm.

tert-Butyl (*S*)-4-((*1R*,*4S*)-1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-13-methyltetradec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (108)

exp: 82
DL630



According to GP 12, the reaction of alkynone **105** (100 mg, 181 µmol) with RuCl[(*S*,*S*)-TsDPEN](mesitylene) (5.76 mg, 9.06 µmol), Et$_3$N (151 µL, 1.09 mmol) and formic acid (34.2 µL, 906 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 80/20), **108** as a reddish oil (62.8 mg, 63 %).

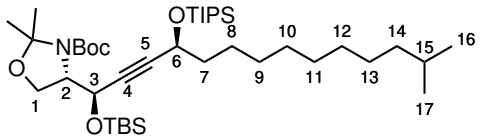
^{1}H-NMR (500 MHz**, $CDCl_3$):** δ = 4.90 – 4.70 (m, 1 H, 3-H), 4.41 – 4.24 (m, 1 H, 6-H), 4.24 – 4.10 (m, 1 H, 1-H), 4.08 – 3.90 (m, 2 H, 1-H, 2-H), 1.72 – 1.57 (m, 2 H, 8-H to 13-H) 1.57 – 1.44 (m, 18 H, 8-H to 13-H, 15-H, Boc–C(C$\underline{H}_3$)$_3$), 1.44 – 1.36 (m, 8 H, 8-H to 13-H, C(C$\underline{H}_3$)$_2$) 1.35 – 1.21 (m, 15 H, 8-H to 13-H), 1.18 – 1.10 (m, 2 H, 14-H) 0.89 (s, 9 H, SiC(C$\underline{H}_3$)$_3$), 0.85 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.12, 0.08 (2s, 2x 3 H, Si(C$\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (126 MHz**, $CDCl_3$):** δ = 152.9 (s, Boc–CO), 94.6 (s, $\underline{C}$(CH$_3$)$_2$), 86.7 (s, C-5), 84.7 (s, C-4), 80.5 (s, Boc–$\underline{C}$(CH$_3$)$_3$), 64.0 (C-1), 62.4 (C-6), 62.3 (C-2), 61.3 (C-3), 39.2 (t, C-14), 37.7 (t, C-7), 30.0, 29.74, 29.70, 29.5, 28.6 (5t, C-8 to C-13), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 26.0 (q, SiC($\underline{C}$H$_3$)$_3$), 25.5, 25.3 (2q, C($\underline{C}$H$_3$)$_2$), 22.8 (q, C-16, C-17), 18.3 (s, Si$\underline{C}$(CH$_3$)$_3$) −4.58, −4.63 (2q, Si($\underline{C}$H$_3$)$_2$) ppm.

HRMS (ESI-TOF): calculated for [M − OTBS]$^+$ $C_{25}H_{44}O_4N$ 422.3265, found 422.3247.

tert-Butyl (*S*)-4-((*5R*,*8S*)-10,10-diisopropyl-2,2,3,3,11-pentamethyl-8-(9-methyldecyl)-4,9-dioxa-3,10-disiladodec-6-yn-5-yl)-2,2-dimethyloxazolidine-3-carboxylate (109)

exp: 83
PRM016



2,6-Lutidine (1.17 mL, 10.1 mmol), 4-DMAP (61.5 mg, 504 µmol) and TIPSOTf (1.49 mL, 5.54 mmol) were added to a solution of alkyne **108** (2.79 g, 5.04 mmol) in CH_2Cl_2 (50.4 mL) at 0 °C and the mixture stirred at r.t. for 16 h. Additional TIPSOTf (300 µL, 1.18 mmol) was added and the reaction stirred for 5 h. Citric acid solution (10 wt − % in H_2O) was added and the aqueous phase extracted with TBME. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 85/15) to yield **109** as a colorless oil (2.85 g, 80 %).

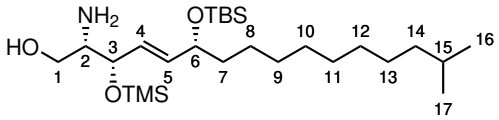
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.57 – 5.37, 5.20 – 5.06 (2m, together 1 H, 3-H), 4.61 – 4.51, 4.51 – 4.41 (2m, 2x 1 H, 2-H, 6-H), 4.27 – 3.96 (m, 2 H, 1-H), 1.84 – 1.72 (m, 3 H, 7-H to 13-H, 15-H, $C(C\underline{H}_3)_2$, Boc−$C(C\underline{H}_3)_3$), 1.71 – 1.54 (m, 2 H, 7-H to 13-H, 15-H, $C(C\underline{H}_3)_2$, Boc−$C(C\underline{H}_3)_3$), 1.46 – 1.40 (m, 7 H, 7-H to 13-H, 15-H, $C(C\underline{H}_3)_2$, Boc−$C(C\underline{H}_3)_3$), 1.37 – 1.24 (m, 6 H, 7-H to 13-H), 1.24 – 1.08 (m, 27 H, 14-H, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$), 1.03 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.94 – 0.76 (m, 6 H, 16-H, 17-H), 0.26, 0.20 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{40}H_{80}NO_5Si_2$ 710.5570, found 710.5555.

4.4.4 Boc-deprotection reactions

(*2S,3S,6R,E*)-2-Amino-6-((*tert*-butyldimethylsilyl)oxy)-15-methyl-3-((trimethylsilyl)oxy)hexadec-4-en-1-ol (113)

exp: 84
DL276



TMSOTf (1.02 mL, 5.67 mmol) was slowly added to a solution of oxazolidine **94** (700 mg, 1.26 mmol) and 2,6-lutidine (1.02 mL, 8.81 mmol) in CH_2Cl_2 (6.30 mL) at 0 °C and the mixture stirred for 30 min. The reaction was quenched by addition of Na_2CO_3 solution and aqueous phase extracted with CH_2Cl_2, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield **113** as a yellowish oil (589 mg, 96 %)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.86 – 5.48 (m, 2 H, 4-H, 5-H), 4.28 – 4.03 (m, 2 H, 3-H, 6-H), 3.81 – 3.49 (m, 3 H, 1-H, 2-H), 1.56 – 1.42 (m, 3 H, 7-H, 15-H), 1.38 – 1.21 (m, 14 H, 8-H to 13-H), 1.19 – 1.10 (m, 2 H, 14-H) 0.89 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.86 (d, J = 6.7 Hz, 6 H, 16-H, 17-H), 0.11 (s, 5 H, $Si(C\underline{H}_3)_3$), 0.05, 0.02 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

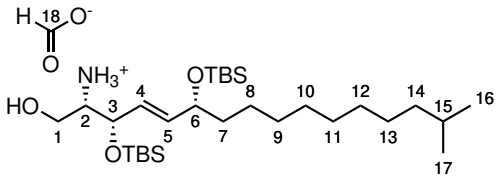
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{26}H_{57}NO_3Si_2$ 488.3950, found 488.3936.

IR (ATR): ν_{max} = 2952, 2925, 2854, 1463, 1250, 1071 cm^{-1}.

$[\alpha]_D^{25}$**:** -5.20° (c = 1.0; $CHCl_3$).

(*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-aminium formate (114)

exp: 85
DL515



According to GP 19, the reaction of oxazolidine **146** (800 mg, 1.44 mmol) with 2,6-lutidine (585 µL, 5.04 mmol), TBSOTf (331 µL, 1.44 mmol) and TMSOTf (520 µL, 2.88 mmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % formic acid 15/85 → 0/100, eluting at 10/90), **114** as a yellowish oil (352 mg, 46 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, 18-H), 5.81 (dd, J = 15.4, 4.8 Hz, 1 H, 5-H), 5.52 (dd, J = 15.5, 7.5 Hz, 1 H, 4-H), 4.29 (t, J = 7.6 Hz, 1 H, 3-H), 4.16 – 4.12 (m, 1 H, 6-H), 3.78 (dd, J = 12.1, 3.4 Hz, 1 H, 1-H), 3.71 – 3.60 (m, 1 H, 1-H), 3.10 – 3.02 (m, 1 H, 2-H), 1.63 – 1.41 (m, 4 H, 7-H to 14-H), 1.41 – 1.21 (m, 15 H, $SiC(C\underline{H}_3)_3$, Boc–$C(C\underline{H}_3)_3$, 7-H to 15-H), 1.21 – 1.11 (m, 2 H, 14-H), 0.91 (s, 18 H, $SiC(C\underline{H}_3)_3$), 0.88 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.12, 0.08, 0.06, 0.03 (4s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 169.2 (d, C-18), 138.8 (d, C-5), 126.9 (d, C-4), 71.9 (d, C-3), 71.8 (d, C-6), 59.3 (t, C-1), 58.1 (d, C-2), 39.0 (t, C-14), 38.1 (t, C-7), 29.9, 29.62, 29.61, 29.58 (t, C-8 to C-13), 27.9 (d, C-14), 27.4 (t, C-8 to C-13), 25.8 (q, $Si(\underline{C}H_3)_2$), 25.2 (t, C-8 to C-13), 22.6 (q, C-16, C-17), 18.1, 18.0 (2 s, $Si\underline{C}(CH_3)_3$), −3.7, −4.3, −4.62, −4.66 (4q, $Si(\underline{C}H_3)_2$) ppm.

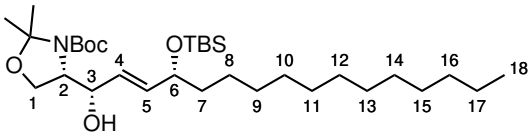
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{29}H_{64}NO_3Si_2$ 530.4419, found 530.4427.

IR (ATR): ν_{max} = 2952, 2926, 2855, 1576, 1252 cm^{-1}.

$[\alpha]_D^{25}$**:** +2.26° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*1S,4R,E*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxyhexadec-2-en-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (115)

exp: 86
DL566



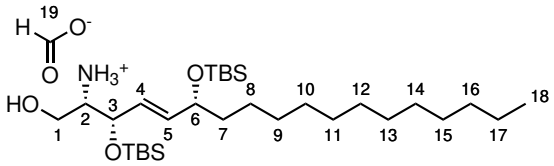
According to GP 17, the reaction of alkynol **79** (310 mg, 915 µmol) with Schwartz' reagent (247 mg, 960 µmol), Et_2Zn (1.16 mL, 1.05 mmol) and Garner's aldehyde **11** (200 mg, 872 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 50/50, eluting at 80/20), **115** as a yellowish oil (302 mg, 61 %).

^{1}H-NMR (500 MHz, C_6D_6): δ = 5.84 (dd, J = 15.4, 6.0 Hz, 1 H, 5-H), 5.73 (dd, J = 15.3, 5.8 Hz, 1 H, 4-H) 4.54 – 4.37 (m, 1 H, 3-H), 4.25 – 4.12 (m, 1 H, 6-H), 4.04 – 3.93 (m, 1 H, 2-H), 3.93 – 3.84 (m, 1 H, 1-H), 3.74 – 3.65 (m, 1 H, 1-H), 1.84 – 1.58 (m, 4 H, 7-H to 17-H), 1.48 – 1.23 (m, 33 H, Boc–$C(C\underline{H}_3)_3$, $C(C\underline{H}_3)_2$, 7-H to 17-H), 1.02 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.94 – 0.87 (m, 3 H, 18-H), 0.13 (s, 6 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz, C_6D_6): δ = 136.9 (d, C-5), 129.0 (d, C-4), 94.6 (s, $\underline{C}(CH_3)_2$), 80.6 (s, Boc–$\underline{C}(CH_3)_3$), 73.4 (d, C-6), 73.3 (d, C-3), 64.7 (t, C-1), 62.7 (d, C-2), 38.8 (t, C-8 to C-16), 32.4 (t, C-7), 30.2, 30.16, 30.13, 29.8 (5t, C-8 to C-16), 28.4 (q, Boc–$C(\underline{C}H_3)_3$), 26.3 (t, C-8 to C-16), 25.6 (q, $C(\underline{C}H_3)_2$, $SiC(\underline{C}H_3)_3$), 23.1 (t, C-17), 18.5 (s, $Si\underline{C}(CH_3)_3$), 14.3 (q, C-18), −3.8, −4.4 (2q, $Si(\underline{C}H_3)_2$) ppm.

(*2S*,*3S*,*6R*,*E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctadec-4-en-2-aminium formate (116)

exp: 87
DL567



According to GP 19, the reaction of oxazolidine **115** (200 mg, 350 µmol) with 2,6-lutidine (143 µL, 1.23 mmol), TBSOTf (80.7 µL, 351 µmol) and TMSOTf (127 µL, 702 µmol) yielded, after flash chromatography (H_2O/ MeOH + 0.1 % formic acid 15/85 → 0/100, eluting at 10/90), **116** as a yellowish oil (162 mg, 78 %).

^{1}H-NMR (500 MHz**, $CDCl_3$):** δ = 8.46 (s, 1 H, 19-H), 5.77 (dd, J = 15.5, 5.1 Hz, 1 H, 5-H), 5.51 (dd, J = 15.5, 7.4 Hz, 1 H, 4-H), 4.24 (t, J = 7.4 Hz, 1 H, 3-H), 4.11 (d, J = 5.9 Hz, 0 H, 6-H), 3.84 – 3.65 (m, 1 H, 1-H), 3.63 – 3.50 (m, 1 H, 1-H), 3.03 – 2.87 (m, 1 H, 2-H), 1.54 – 1.39 (m, 2 H, 7-H to 17-H), 1.35 – 1.17 (m, 24 H, $C(C\underline{H}_3)_2$, Boc–$C(C\underline{H}_3)_3$, 7-H to 17-H), 0.91 – 0.84 (m, 20 H, $SiC(C\underline{H}_3)_3$, 18-H), 0.10, 0.06, 0.04, 0.01 (4s, 4x 3 H, $Si(C\underline{H}_3)_2$) ppm.

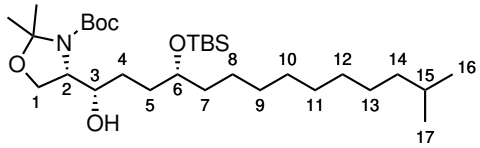
^{13}C-NMR (126 MHz**, $CDCl_3$):** δ = 169.2 (d, C-19), 138.7 (d, C-5), 127.4 (d, C-4), 72.6 (d, C-6), 72.0 (d, C-3), 60.2 (t, C-1), 58.3 (d, C-2), 38.3 (t, C-7), 32.1, 29.85, 29.80, 29.76, 29.5 (5t, C-8 to C-16), 26.02, 26.00 (2q, $Si(\underline{C}H_3)_2$), 25.4 (t, C-8 to C-16), 22.8 (t, C-17), 18.2 (s, $Si\underline{C}(CH_3)_3$), 14.3 (C-18), −3.6, −4.2, −4.5, −4.6 (4q, $Si(\underline{C}H_3)_2$) ppm.

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{30}H_{66}NO_3Si_2$ 544.4579, found 544.4555.

IR (ATR): ν_{max} = 2952, 2926, 2855, 1652, 1463, 1253, 1218 cm^{-1}.

tert-Butyl (*4S*)-4-((*1S*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradecyl)-2,2-dimethyloxazolidine-3-carboxylate (SI-16)

exp: 88
DL422



According to GP 8, the reaction of oxazolidine **94** (2.00 g, 3.60 mmol) with Pd/C (382 mg, 359 µmol) in H_2-atmosphere yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 6/1, eluting at 6/1), **SI-16** as a colorless oil (1.78 g, 89 %).

^{1}H-NMR (500 MHz**, $CDCl_3$):** δ = 4.03 – 3.85 (m, 2 H, 3-H, 6-H), 3.84 – 3.74 (m, 1 H, 1-H), 3.74 – 3.61 (m, 2 H, 1-H, 2-H), 1.68 – 1.55 (m, 4 H, 4-H, 5-H), 1.54 – 1.47 (m, 14 H, 7-H, 15-H, $C(C\underline{H}_3)_2$), 1.42 (s, 9 H, Boc–$C(C\underline{H}_3)_3$), 1.32 – 1.20 (m, 15 H, 8-H to 13-H), 1.18 – 1.10 (m, 2 H, 14-H), 0.87 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.85 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.03 (s, 6 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz**, $CDCl_3$):** δ = 155.3 (s, Boc–CO), 94.1 (s, $\underline{C}(CH_3)_2$), 81.4 (s, Boc–$\underline{C}(CH_3)_3$), 74.4 (d, C-3), 72.4 (d, C-6), 65.0 (t, C-1), 62.5 (d, C-2), 39.2 (t, C-14), 37.2 (t, C-7), 33.8, 32.4 (2t, C-4, C-5), 30.04, 29.98, 29.8 (3t, C-8 to C-13), 28.5 (q, $SiC(\underline{C}H_3)_3$), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 26.1 (q, $C(\underline{C}H_3)_2$), 25.5 (t, C-8 to C-13), 22.8 (q, C-16, C-17), 18.2 (s, $Si\underline{C}(CH_3)_3$), −4.3 (q, $Si(\underline{C}H_3)_2$) ppm.

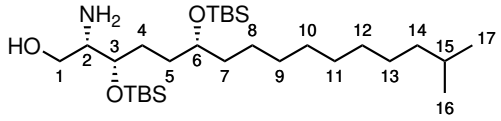
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{31}H_{64}NO_5Si$ 558.4548, found 558.4538.

IR (ATR): ν_{max} = 2952, 2925, 2854, 1698, 1670, 1462, 1365, 1252, 1059 cm^{-1}.

$[\alpha]_D^{25}$**:** -25.2° (c = 1.0; $CHCl_3$).

(*2S,3S,6R*)-2-Amino-3,6-bis((*tert*-butyldimethylsilyl)oxy)-15-methylhexadecan-1-ol (117)

exp: 89
DL454



According to GP 19, the reaction of oxazolidine **SI-16** (1.00 g, 1.79 mmol) with 2,6-lutidine (622 µL, 5.36 mmol), TBSOTf (453 µL, 1.97 mmol) and TMSOTf (645 µL, 3.57 mmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % formic acid 15/85 → 0/100, eluting at 10/90), **117** as a colorless oil (479 mg, 50 %).

^{1}H-NMR (500 MHz**, CDCl$_3$):** δ = 3.68 – 3.53 (m, 3 H, 1-H, 3-H, 6-H), 3.45 – 3.39 (m, 1 H, 1-H), 2.88 – 2.79 (m, 1 H, 2-H), 1.63 – 1.46 (m, 3 H, 7-H, 15-H), 1.46 – 1.35 (m, 4 H, 4-H 5-H), 1.32 – 1.20 (m, 13 H, 8-H to 13-H), 1.19 – 1.11 (m, 2 H, 14-H), 0.89, 0.88 (2s, 2x 9 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.7 Hz, 6 H, 16-H, 17-H), 0.07, 0.06, 0.04, 0.03 (4s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (126 MHz**, CDCl$_3$):** δ = 73.4 (d, C-3), 72.4 (d, C-6), 64.4 (t, C-1), 55.5 (d, C-2), 39.2 (t, C-14), 37.5, 32.5 (2t, C-4, C-5), 30.1, 30.01, 29.95, 29.8 (4t, C-8 to C-13), 28.1 (d, C-15), 27.6 (t, C-8 to C-13), 26.1, 26.0 (2q, SiC($\underline{C}H_3$)$_3$), 25.4 (t, C-8 to C-13), 22.8 (q, C-16, C-17), 18.25, 18.20 (2s, Si$\underline{C}$(CH$_3$)$_3$), −3.9, −4.2, −4.3, −4.5 (4q, Si($\underline{C}H_3$)$_2$) ppm.

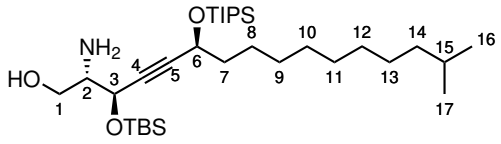
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{29}H_{66}NO_3Si_2$ 532.4576, found 532.4559.

IR (ATR): ν_{max} = 2952, 2926, 2855, 1253, 1065 cm^{-1}.

$[\alpha]_D^{25}$**:** -0.17° (c = 1.0; $CHCl_3$).

(*2S,3R,6S*)-2-Amino-3-((*tert*-butyldimethylsilyl)oxy)-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yn-1-ol (118)

exp: 90
DL730



According to GP 19, the reaction of oxazolidine **109** (187 mg, 263 µmol) with 2,6-lutidine (76.4 µL, 658 µmol) and TMSOTf (95.1 µL, 527 mmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % formic acid 15/85 → 0/100, eluting at 10/90), **118** as a colorless oil (75.0 mg, 50 %).

^{1}H-NMR (500 MHz**, CDCl$_3$):** δ = 4.56 – 4.46 (m, 1 H, 6-H), 4.46 – 4.38 (m, 1 H, 3-H), 3.84 – 3.55 (m, 2 H, 1-H), 3.01 – 2.83 (m, 1 H, 2-H), 1.81 – 1.58 (m, 2 H, 7-H), 1.57 – 1.18 (m, 12 H, 8-H to 12-H, 15-H), 1.18 – 0.97 (m, 23 H, 13-H, SiCH($C\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.89 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.87 – 0.83 (m, 6 H, 16-H, 17-H) 0.14, 0.11 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (75 MHz**, CDCl$_3$):** δ = 88.7 (s, C-5), 82.0 (s, C-4), 65.8 (d, C-6), 63.2 (d, C-3), 62.6 (t, C-1), 57.8 (d, C-2), 39.2 (t, C-14), 39.0 (t, C-7), 30.0, 29.7, 29.5 (3t, C-8 to C-13), 28.1 (d, C-15) 25.8

(q, SiC($\underline{C}H_3)_3$), 25.1 (t, C-8 to C-13), 22.8 (q, C-16, C-17), 18.2 (q, s, SiCH($\underline{C}H_3)_2$, Si$\underline{C}(CH_3)_3$), 12.4 (d, Si$\underline{C}H(CH_3)_2$), −4.4, −5.1 (2q, Si($\underline{C}H_3)_2$) ppm.

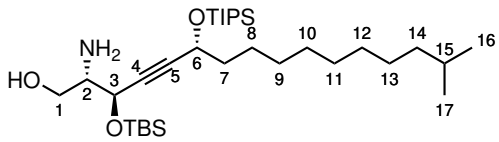
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{32}H_{68}O_3NSi_2$ 570.4732, found 570.4737.

IR (ATR): ν_{max} = 2926, 2863, 1462, 1251, 1089 cm^{-1}.

$[\alpha]_D^{25}$**:** -42.7° ($c = 1.0$; $CHCl_3$).

(*2S,3R,6R*)-2-Amino-3-((*tert*-butyldimethylsilyl)oxy)-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yn-1-ol (119)

exp: 91
DL745



According to GP 19, the reaction of oxazolidine **107** (600 mg, 845 µmol) with 2,6-lutidine (245 µL, 2.11 mmol), 4-DMAP (10.3 mg, 84.5 µmol) and TMSOTf (305 µL, 1.69 mmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % formic acid 15/85 → 0/100, eluting at 10/90), **119** as a colorless oil (366 mg, 69 %).

^{1}H-NMR (300 MHz**, $CDCl_3$):** δ = 4.57 – 4.45 (m, 2 H, 3-H, 6-H), 3.83 – 3.67 (m, 2 H, 1-H), 3.11 – 3.00 (m, 1 H, 2-H), 1.67 (p, J = 6.5, 5.5 Hz, 2 H, 7-H), 1.58 – 1.36 (m, 2 H, 8-H to 12-H), 1.31 – 1.22 (m, 9 H, 8-H to 12-H, 15-H), 1.18 – 1.00 (m, 24 H, 13-H, SiCH($C\underline{H}_3)_2$, Si$\underline{C}H(CH_3)_2$), 0.90 (s, 9 H, SiC($C\underline{H}_3)_3$), 0.85 (t, J = 6.7 Hz, 3 H, 16-H, 17-H), 0.15, 0.13 (2s, 2x 3 H, Si($C\underline{H}_3)_2$) ppm.

^{13}C-NMR (75 MHz**, $CDCl_3$):** δ = 89.2 (s, C-5), 81.7 (s, C-4), 65.1 (d, C-6), 63.2 (d, C-3), 62.1 (t, C-1), 57.7 (d, C-2), 39.2 (t, C-14), 39.0 (t, C-7), 30.1, 29.8, 29.5 (3t, C-8 to C-13), 28.1 (d, C-15), 25.9 (SiC($\underline{C}H_3)_3$), 25.1 (t, C-8 to C-13), 22.8 (q, C-16, C-17), 18.2 (q, s, SiCH($\underline{C}H_3)_2$, Si$\underline{C}(CH_3)_3$), 12.4 (d, Si$\underline{C}H(CH_3)_2$), −4.4, −5.0 (2q, Si($\underline{C}H_3)_2$) ppm.

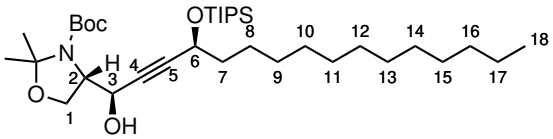
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{32}H_{68}NO_3Si_2$ 570.4732, found 570.4722.

IR (ATR) ν_{max}: 2926, 2863, 1462, 1252, 1086, 1063 cm^{-1}.

$[\alpha]_D^{25}$**:** -15.9° ($c = 1.0$; $CHCl_3$).

tert-Butyl (*S*)-4-((*1R,4S*)-1-hydroxy-4-((triisopropylsilyl)oxy)hexadec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (120)

exp: 92
DL764



A solution of *n*-BuLi in hexanes (1.19 µL, 2.20 M, 2.62 mmol) was added dropwise to a solution of silyl ether (797 mg, 2.09 mmol) in THF (4.19 mL) at −78 °C and the mixture stirred for 35 min. DMPU (1.90 mL, 15.7 mmol) and Garner's aldehyde **11** (400 mg, 1.74 mmol) in THF (3.49 mL) were added slowly at −78 °C. The reaction was stirred at −78 °C for 30 min, the cooling bath removed and the reaction stirred at r.t. for 16 h. Sat. NH_4Cl solution was added, the aqueous phase extracted with TBME, the combined organic phase washed with H_2O, brine and dried over $MgSO_4$. The extract was filtered, the

volatiles removed *in vacuo* and the crude product purified *via* flash chromatography (cyclohexane/EtOAc 100/0 → 50/50, eluting at 85/15) to yield **120** as a yellowish oil (503 mg, 47 %, d.r. >19:1).

^{1}H-NMR (300 MHz, C_6D_6): δ = 4.85 – 4.65 (m, 1 H), 4.59 (td, J = 6.2, 1.5 Hz, 1 H, 3-H, 6-H), 4.09 – 3.97 (m, 1 H, 1-H, 2-H), 3.85 – 3.74 (m, 1 H, 1-H), 1.90 – 1.72 (m, 2 H, 7-H), 1.72 – 1.57 (m, 4 H, 8-H to 17-H, C(C$\underline{H}_3$)$_2$), 1.49 – 1.26 (m, 18 H, 8-H to 17-H, Boc–C(C$\underline{H}_3$)$_3$, C(C$\underline{H}_3$)$_2$), 1.23 – 1.08 (m, 21 H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.94 – 0.84 (m, 3 H, 18-H) ppm. The Spectrum was measured at 50 °C.

^{13}C-NMR (75 MHz, C_6D_6): δ = 154.2 (s, Boc–CO), 95.2 (s, $\underline{C}$(CH$_3$)$_2$), 88.0 (s, C-5), 83.4 (s, C-4), 80.6 (s, Boc–$\underline{C}$(CH$_3$)$_3$), 65.1 (t, C-1), 64.0, 63.7 (2d, C-3, C-6), 62.9 (d, C-2), 39.5 (t, C-7), 32.3, 30.2, 30.12, 30.08, 29.9, 29.8 (6t, C-8 to C-17), 28.4 (q, Boc–C($\underline{C}$H$_3$)$_3$), 26.4 (q, C($\underline{C}$H$_3$)$_2$), 25.5, 23.1 (2t, C-8 to C-17), 18.4 (q, SiCH($\underline{C}$H$_3$)$_2$), 14.3 (q, C-18), 12.8 (d, Si$\underline{C}$H(CH$_3$)$_2$) ppm.

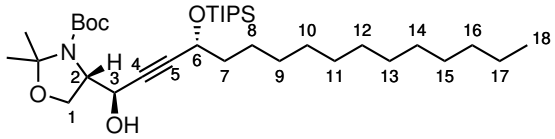
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{35}H_{68}NO_5Si$ 610.4861, found 610.4848.

IR (ATR) ν_{max}: 2924, 2863, 1696, 1457, 1392, 1366, 1246, 1170, 1085, 1065 cm^{-1}.

$[\alpha]_D^{25}$**:** -34.5° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*1R,4R*)-1-hydroxy-4-((triisopropylsilyl)oxy)hexadec-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (121)

exp: 93
DL763



A solution of *n*-BuLi in hexanes (892 µL, 2.20 M, 1.96 mmol) was added dropwise to a solution of silyl ether (598 mg, 1.57 mmol) in THF (3.14 mL) at −78 °C and the mixture stirred for 20 min. DMPU (1.42 mL, 11.8 mmol) and Garner's aldehyde **11** (300 mg, 1.31 mmol) in THF (2.62 mL) were added slowly at −78 °C. The reaction was stirred at −78 °C for 30 min, the cooling bath removed and the reaction stirred at r.t. for 16 h. Sat. NH_4Cl solution was added, the aqueous phase extracted with TBME, the combined organic phase washed with H_2O, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified *via* flash chromatography (cyclohexane/EtOAc 100/0 → 50/50, eluting at 85/15) to yield **121** as a yellowish oil (375 mg, 47 %, d.r. >19:1).

^{1}H-NMR (300 MHz, C_6D_6): δ = 4.84 – 4.69 (m, 1 H), 4.60 (td, J = 6.2, 1.5 Hz, 1 H, 3-H, 6-H), 4.10 – 3.98 (m, 1 H, 1-H, 2-H), 3.84 – 3.70 (m, 1 H, 1-H), 1.81 (dt, J = 8.9, 6.3 Hz, 2 H, 7-H), 1.76 – 1.53 (m, 4 H, 8-H to 17-H, C(C$\underline{H}_3$)$_2$), 1.50 – 1.41 (m, 6 H, 8-H to 17-H,C(C$\underline{H}_3$)$_2$), 1.39 (s, 9 H, Boc–C(C$\underline{H}_3$)$_3$), 1.36 – 1.26 (m, 18 H, 8-H to 17-H), 1.23 – 1.08 (m, 21 H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.94 – 0.87 (m, 3 H, 18-H) ppm. The Spectrum was measured at 50 °C; one proton-signal/integration is missing in the 1-position.

^{13}C-NMR (75 MHz, C_6D_6): δ = 154.3 (s, Boc–CO), 95.2 (s, $\underline{C}$(CH$_3$)$_2$), 88.0 (s, C-5), 83.5 (s, C-4), 80.6 (s, Boc–$\underline{C}$(CH$_3$)$_3$), 65.1 (t, C-1), 64.2, 63.8 (2d, C-3, C-6), 62.9 (d, C-2), 39.5 (t, C-7), 32.3, 30.2, 30.12, 30.06, 29.9, 29.8 (6t, C-8 to C-17), 28.4 (q, Boc–C($\underline{C}$H$_3$)$_3$), 26.4 (q, C($\underline{C}$H$_3$)$_2$), 25.5, 23.1 (2t, C-8 to C-17), 18.4 (q, SiCH($\underline{C}$H$_3$)$_2$), 14.3 (q, C-18), 12.8 (d, Si$\underline{C}$H(CH$_3$)$_2$) ppm.

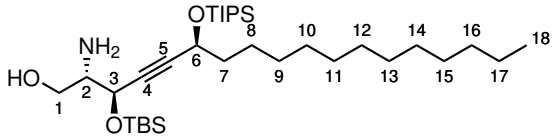
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{35}H_{68}NO_5Si$ 610.4861, found 610.4842.

IR (ATR) ν_{max}: 2924, 2863, 1696, 1457, 1392, 1366, 1247, 1170, 1086, 1065 cm^{-1}.

$[\alpha]_D^{25}$**:** -5.97° (c = 2.0; $CHCl_3$).

(*2S,3R,6S*)-2-Amino-3-((*tert*-butyldimethylsilyl)oxy)-6-((triisopropylsilyl)oxy)-octadec-4-yn-1-ol (122)

exp: 94
DL769



According to GP 19, the reaction of oxazolidine **120** (340 mg, 557 µmol) with 2,6-lutidine (458 µL, 3.95 mmol), 4-DMAP (6.81 mg, 55.7 µmol), TBSOTf (204 µL, 888 µmol) and TMSOTf (391 µL, 2.16 mmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % formic acid 15/85 → 0/100, eluting at 10/90), **122** as a colorless oil (183 mg, 56 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.53 – 4.45 (m, 2 H, 3-H, 6-H), 4.41 (s, 4 H, N-H, O-H), 3.81 – 3.61 (m, 2 H, 1-H), 3.01 (dt, J = 6.9, 4.5 Hz, 1 H, 2-H), 1.67 (dt, J = 9.8, 6.4 Hz, 2 H, 7-H), 1.51 – 1.35 (m, 2 H, 8-H to 17-H), 1.26 (d, J = 6.3 Hz, 21 H, 8-H to 17-H), 1.16 – 0.99 (m, 23 H, SiCH($C\underline{H}_3$)$_2$, Si$\underline{C}$H(CH_3)$_2$), 0.88 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.88 – 0.82 (m, 3 H, 18-H), 0.14, 0.11 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 89.0 (s, C-5), 81.6 (s, C-4), 65.0 (d, C-6), 63.2 (d, C-3), 61.9 (t, C-1), 57.8 (d, C-2), 39.0 (t, C-7), 32.1, 29.81, 29.78, 29.7, 29.51, 29.49 (5t, C-8 to C-17), 25.8 (q, SiC($\underline{C}H_3$)$_3$), 25.1, 22.8 (2t, C-8 to C-17), 18.2 (q+s, SiCH($\underline{C}H_3$)$_2$,Si$\underline{C}$(CH_3)$_3$), 14.2 (q, C-18), 12.4 (d, Si$\underline{C}$H(CH_3)$_2$), −4.5, −5.1 (2q, Si($\underline{C}H_3$)$_2$) ppm.

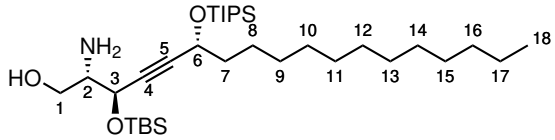
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{33}H_{69}NNaO_3Si_2$ 606.4708, found 606.4712.

IR (ATR) ν_{max}: 2924, 2855, 1463, 1251, 1089, 1063 cm^{-1}.

$[\alpha]_D^{25}$**:** -33.6° (c = 1.0; $CHCl_3$).

(*2S,3R,6R*)-2-amino-3-((*tert*-Butyldimethylsilyl)oxy)-6-((triisopropylsilyl)oxy)-octadec-4-yn-1-ol (123)

exp: 95
DL768



According to GP 19, the reaction of oxazolidine **121** (320 mg, 525 µmol) with 2,6-lutidine (444 µL, 3.82 mmol), 4-DMAP (6.41 mg, 52.5 µmol), TBSOTf (196 µL, 853 µmol) and TMSOTf (389 µL, 2.15 mmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % formic acid 15/85 → 0/100, eluting at 10/90), **123** as a colorless oil (82.6 mg, 27 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.56 – 4.38 (m, 2 H, 3-H, 6-H), 3.81 – 3.58 (m, 2 H, 1-H), 3.56 (s, 4 H, N-H, O-H), 2.96 (dt, J = 6.7, 4.7 Hz, 1 H, N-H), 1.72 – 1.59 (m, 2 H, 7-H), 1.49 – 1.36 (m, 2 H, 8-H to 17-H), 1.28 – 1.22 (m, 25 H, 8-H to 17-H), 1.10 – 1.02 (m, 28 H, SiCH($C\underline{H}_3$)$_2$, Si$\underline{C}$H(CH_3)$_2$), 0.89 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.91 – 0.82 (m, 3 H, 18-H), 0.14, 0.11 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 88.9 (s, C-5), 82.1 (s, C-4), 65.6 (d, C-6), 63.2 (d, C-3), 62.5 (t, C-1), 57.8 (d, C-2), 39.0 (t, C-7), 32.1, 29.82, 29.79, 29.7, 29.52, 29.50 (6t, C-8 to C-17), 25.8 (q, SiC($\underline{C}H_3$)$_3$), 25.1, 22.8 (2t, C-8 to C-17), 18.2 (q+s, SiCH($\underline{C}H_3$)$_2$, Si$\underline{C}$(CH_3)$_3$), 14.2 (q, C-18), 12.4 (d, Si$\underline{C}$H(CH_3)$_2$), −4.4, −5.1 (2q, Si($\underline{C}H_3$)$_2$) ppm.

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{33}H_{70}NO_3Si_2$ 584.4889, found 584.4904.

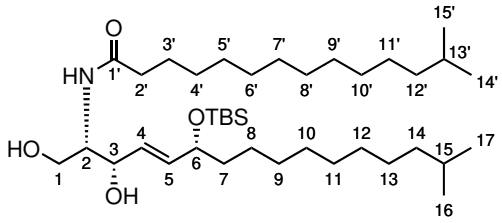
IR (ATR) ν_{max}: 2924, 2855, 1463, 1251, 1089, 1063 cm^{-1}.

$[\alpha]_D^{25}$**:** -8.17° ($c = 1.0$; $CHCl_3$).

4.4.5 Synthesis of unnatural ceramides

N-((*2S,3S,6R,E*)-6-((*tert*-Butyldimethylsilyl)oxy)-1,3-dihydroxy-15-methylhexadec-4-en-2-yl)-13-methyltetradecanamide (124)

exp: 96
DL272



According to GP 21, the reaction of amine **113** (100 mg, 168 µmol) with carboxylic acid **34** (53.0 mg, 218 µmol), EDC (48.3 mg, 252 µmol), HOBt·H_2O (54.07 mg, 336 µmol) and DIPEA (142 µL, 840 µmol) yielded, after flash chromatography (CH_2Cl_2/*i*-PrOH 97/3 → 90/10, eluting at 95/5), **124** as a yellowish oil (38 mg, 36 %).

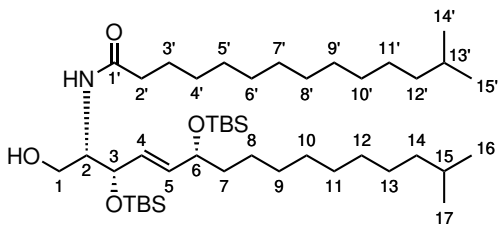
^{1}**H-NMR** (500 MHz, $\mathbf{CDCl_3}$)**:** δ = 6.34 (d, J = 7.0 Hz, 1 H, N-H), 5.77 (dd, J = 14.6, 4.9 Hz, 1 H, 5-H), 5.69 – 5.53 (m, 1 H, 4-H), 4.36 (dd, J = 16.2, 5.2 Hz, 1 H, 3-H), 4.19 – 4.07 (m, 1 H, 6-H), 3.95 – 3.85 (m, 2 H, 1-H, 2-H), 3.82 – 3.61 (m, 1 H, 1-H), 2.20 (t, J = 7.6 Hz, 2 H, 2'-H), 1.69 – 1.56 (m, 3 H, 7-H to 11-H, 3'-H to 11'-H), 1.56 – 1.40 (m, 5 H, 7-H to 11-H, 3'-H to 11'-H, 15-H, 13'-H), 1.40 – 1.19 (m, 35 H, 7-H to 11-H, 3'-H to 11'-H), 1.19 – 1.09 (m, 4 H, 14-H, 12'-H), 0.89 (s, 9 H, $SiC(\underline{C}H_3)_3$), 0.85 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.04, 0.01 (2s, 2x 3 H, $Si(\underline{C}H_3)_2$) ppm.

^{13}**C-NMR** (126 MHz, $\mathbf{CDCl_3}$)**:** δ = 174.2 (s, C-1'),136.6 (d, C-5'), 128.1 (d, C-4'), 74.0 (d, C-3), 72.6 (d, C-6), 62.5 (t, C-1), 54.6 (d, C-2), 39.2 (t, C-14, C-12'), 38.4 (t, C-7), 37.0 (t, C-2'), 30.09, 30.05, 29.9, 29.8, 29.7, 29.53, 29.47 (7t, C-8 to C-13, C-4' to C-11'), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.0 (q, $SiC(\underline{C}H_3)_3$), 22.8 (q, C-16, C-17, C-14', C-15'), −4.1, −4.6 (2q, $Si(\underline{C}H_3)_2$) ppm.

IR (ATR): ν_{max} = 3342, 2924, 2853, 1743, 1508, 1464, 1239, 1046 cm^{-1}.

N-((*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)-13-methyltetradecanamide (125)

exp: 97
DL517



According to GP 22, the reaction of amine **114** (40 mg, 69.4 µmol) with carboxylic acid **34** (18.5 mg, 76.4 µmol), DCC (18.6 mg, 90.3 µmol) and DIPEA (13.3 µL, 76.4 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 55/45), **125** as a yellowish oil (18.6 mg, 35 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.93 (d, J = 7.4 Hz, 1 H, N-H), 5.68 (dd, J = 15.5, 5.3 Hz, 1 H, 5-H), 5.59 (dd, J = 15.5, 5.9 Hz, 1 H, 4-H), 4.39 (dd, J = 6.0, 2.8 Hz, 1 H, 3-H), 4.09 (t, J = 5.8 Hz, 1 H, 6-H), 3.92 – 3.84 (m, 1 H, 2-H), 3.72 (dd, J = 10.8, 6.3 Hz, 1 H, 1-H), 3.63 (dd, J = 11.0, 5.5 Hz, 1 H, 1-H), 2.19 (t, J = 7.7 Hz, 2 H, 2'-H), 1.75 – 1.56 (m, 6 H, 7-H to 13-H, 3'-H to 11'-H), 1.56 – 1.40 (m, 5 H, 7-H to 15-H, 3'-H to 13'-H), 1.38 – 1.19 (m, 30 H, 7-H to 13-H, 3'-H to 11'-H), 1.19 – 1.09 (m, 5 H, 14-H, 12'-H), 0.91, 0.89 (2s, 2x 9 H, $SiC(C\underline{H}_3)_3$), 0.86 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14-H, 15-H), 0.09, 0.06, 0.03, 0.00 (4s, 4x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 174.2 (s, C-1'), 136.0 (d, C-5), 128.9 (d, C-4), 72.4 (d, C-6), 71.7 (d, C-3), 64.1 (t, C-1), 56.5 (d, C-2), 39.2 (t, C-14, C-12'), 38.5 (t, C-7), 36.9 (t, C-2'), 30.11, 30.07, 29.9, 29.81, 29.78, 29.7, 29.6, 29.5 29.4 (9t, C-8 to C-13, C-3' to C-11'), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-3' to C-11'), 26.0 (q, $Si(\underline{C}H_3)_2$), 25.8, 25.4 (2t, C-8 to C-13, C-3' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.3, 18.2 (2s, $Si\underline{C}(CH_3)_3$), −4.0, −4.2, −4.7, −4.9 (4q, $Si(\underline{C}H_3)_2$) ppm.

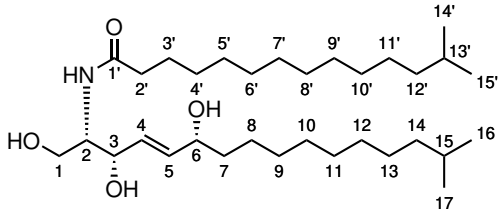
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{44}H_{91}NNaO_4Si_2$ 776.6379, found 776.6397.

IR (ATR): ν_{max} = 2926, 2855, 1652, 1507 cm^{-1}.

$[\alpha]_D^{25}$**:** -0.99° (c = 1.0; $CHCl_3$).

13-Methyl-*N*-((*2S,3S,6R,E*)-1,3,6-trihydroxy-15-methylhexadec-4-en-2-yl)tetradecanamide (126)

exp: 98
DL537



According to GP 23, the reaction of amide **125** (16.7 mg, 22.1 µmol) with TBAF (48.7 µL, 48.7 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 0/100), **126** as a colorless solid (2.6 mg, 22 %).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.16 (d, J = 8.0 Hz, 1 H, N-H), 5.80 (dd, J = 15.5, 5.9 Hz, 1 H 5-H) 5.71 (dd, J = 15.5, 5.6 Hz, 1 H, 4-H) 4.50 – 4.46 (m, 1 H, 3-H), 4.11 (q, J = 6.3 Hz, 1 H, 6-H), 3.97 – 3.91 (m, 1 H, 2-H), 3.86 (dd, J = 11.1, 4.0 Hz, 1 H, 1-H), 3.80 (dd, J = 11.1, 4.6 Hz, 1 H, 1-H), 2.22 (t, J = 7.7 Hz, 2 H, 2'-H), 1.80 – 1.22 (m, 34 H, 7-H to 15-H, 3'-H to 13'-H), 1.18 – 1.08 (m, 4 H, 7-H to 15-H, 3'-H to 13'-H), 0.89 (d, J = 6.6 Hz, 12 H, 16-H, 17, 14'-H, 15'-H-H) ppm.

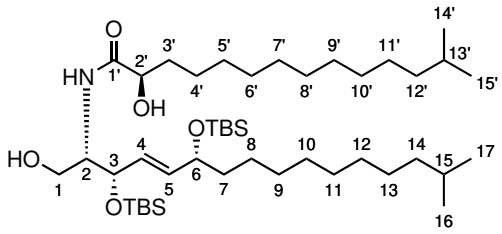
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{32}H_{63}NNaO_4$ 548.4649, found 548.4627.

IR (ATR): ν_{max} = 2917, 2848, 1698, 1540, 1219 cm^{-1}.

$[\alpha]_D^{25}$**:** -8.52° (c = 0.1; $CHCl_3$).

(*R*)-*N*-((*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)-2-hydroxy-13-methyltetradecanamide (127)

exp: 99
DL597



According to GP 21, the reaction of amine **114** (10.0 mg, 17.4 µmol) with carboxylic acid **43** (4.93 mg, 19.1 µmol), HBTU (11.2 mg, 29.5 µmol) and DIPEA (7.56 µL, 43.4 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 50/50), **127** as a colorless oil (6.4 mg, 47 %).

^{1}H-NMR (300 MHz**, $CDCl_3$):** δ = 6.87 (d, J = 7.6 Hz, 1 H, N-H), 5.70 (dd, J = 15.6, 5.1 Hz, 1 H, 5-H), 5.58 (dd, J = 15.6, 6.0 Hz, 1 H, 4-H), 4.40 (dd, J = 6.1, 3.1 Hz, 1 H, 3-H), 4.10 (dd, J = 7.7, 4.1 Hz, 2 H, 6-H, 2'-H), 3.88 (dtd, J = 8.9, 5.9, 3.0 Hz, 1 H, 2-H), 3.70 (dd, J = 5.9, 4.7 Hz, 2 H, 1-H), 2.10 – 1.97 (m, 1 H, 3'-H), 1.89 – 1.75 (m, 1 H, 3'-H), 1.74 – 1.36 (m, 6 H, 7-H to 15-H, 4'-H to 13'-H), 1.36 – 1.19 (m, 36 H, 7-H to 13-H, 4'-H to 11'-H), 1.19 – 1.01 (m, 4 H, 14-H, 12'-H), 0.91, 0.89 (2s, 2x 9 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.10, 0.06, 0.04, 0.01 (4s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (75 MHz**, $CDCl_3$):** δ = 174.8 (s, C-1'), 136.3 (d, C-5), 128.6 (d, C-4), 72.4 (d, C-6), 72.3 (d, C-2'), 71.8 (d, C-3), 63.7 (t, C-1), 56.4 (d, C-2), 39.2 (t, C-14, C-12'), 38.5 (t, C-7), 35.1 (t, C-3'), 32.0, 30.1, 29.9, 29.82, 29.78, 29.72, 29.69, 29.55, 29.51, 29.46 (10t, C-8 to C-13, C-4' to C-11'), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.02,25.96 (2q, SiC($\underline{C}H_3$)$_3$), 25.4, 25.3 (2t, C-8 to C-13, C-4' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.4, 18.2 (2s, Si$\underline{C}$(CH$_3$)$_3$), −3.9, −4.2, −4.6, −4.9 (4q, Si($\underline{C}H_3$)$_2$) ppm.

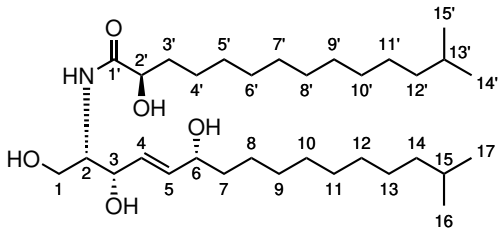
HRMS (ESI-TOF): calculated for [M − OTBS]$^+$ $C_{42}H_{84}NO_4Si$ 694.6164, found 694.6134.

IR (ATR): ν_{max} = 2954, 2924.2853, 1652, 1252, 1082 cm^{-1}.

$[\alpha]_D^{25}$**:** +8.65° (c = 0.6; $CHCl_3$).

(*R*)-2-Hydroxy-13-methyl-*N*-((*2S*,*3S*,*6R*,*E*)-1,3,6-trihydroxy-15-methylhexadec-4-en-2-yl)tetradecanamide (128)

exp: 100
DL609



According to GP 24, the reaction of amide **127** (5.4 mg, 7.01 µmol) with HF·pyridine (14.6 µL, 17.5 µmol) yielded, after preparative RP-TLC (H_2O/MeCN 5/95, R_f=0.5), **128** as a colorless oil (0.4 mg, 11 %).

^{1}H-NMR (600 MHz**, DMSO−d_6):** δ = 7.11 (d, J = 8.8 Hz, 1 H, N-H), 5.59 (s, 1 H, O-H), 5.53 (dd, J = 15.7, 5.7 Hz, 1 H, 5-H), 5.46 (dd, J = 15.6, 5.7 Hz, 1 H, 4-H), 5.12 (s, 1 H, O-H), 4.71 (s, 1 H, O-H), 4.56 (s, 1 H, O-H), 4.32 – 4.22 (m, 1 H, 3-H), 3.86 – 3.75 (m, 2 H, 6-H, 2'-H), 3.65 (tdd, J = 8.1, 5.3, 2.5 Hz, 1 H, 2-H), 1.64 – 1.53 (m, 2 H, 7-H to 13-H, 3'-H to 11'-H), 1.53 – 1.38 (m, 2 H, 7-H to 15-H, 3'-H to 13'-H), 1.38 – 1.16 (m, 44 H, 7-H to 13-H, 3'-H to 11'-H), 1.16 – 1.03 (m, 4 H, 14-H, 12'-H), 0.84 (d, J = 6.6 Hz, 12 H, 16-H,17-H, 14'-H, 15'-H) ppm.

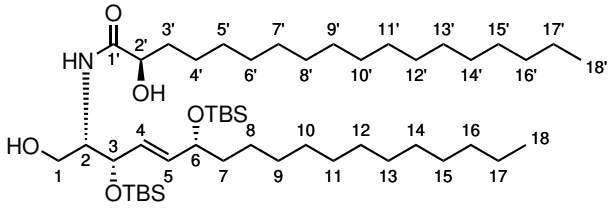
^{13}C-NMR (151 MHz, DMSO−d_6): δ = 173.6 (s, C-1'), 134.4 (d, C-5), 129.8 (d, C-4), 71.0, 70.4 (2d, C-6, C-2'), 67.9 (d, C-3), 60.1 (t, C-1), 54.3 (d, C-2), 38.5 (t, C-14, C-12'), 37.4 (t, C-7), 34.4 (t, C-3'), 31.4, 29.4, 29.3, 29.20, 29.17, 29.12, 29.05, 29.01, 28.8 (8t, C-8 to C-13, C-4' to C-11'), 27.4 (d, C-15, C-13'), 26.8, 25.2, 24.6 (3t, C-8 to C-13, C-4' to C-11'), 22.5 (q, C-16, C-17, C-14', C-15') ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{32}H_{63}NNAO_5$ 564.4598, found 564.4606.

$[\alpha]_D^{25}$**:** -70.7° ($c = 0.04$; MeOH).

(*R*)-*N*-((*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxyoctadec-4-en-2-yl)-2-hydroxyoctadecanamide (129)

exp: 101
DL596



According to GP 21, the reaction of amine **116** (15.0 mg, 25.4 µmol) with carboxylic acid **44** (8.40 mg, 28.0 µmol), HBTU (16.4 mg, 43.2 µmol) and DIPEA (11.1 µL, 63.6 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0→ 0/100, eluting at 50/50), **129** as a colorless oil (5.2 mg, 25 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.86 (d, J = 7.6 Hz, 1 H, N-H), 5.70 (dd, J = 15.6, 5.1 Hz, 1 H, 5-H), 5.59 (dd, J = 15.6, 5.8 Hz, 1 H, 4-H), 4.40 (dd, J = 6.1, 3.0 Hz, 1 H, 3-H), 4.17 – 4.05 (m, 2 H, 6-H, 2'-H), 3.92 – 3.83 (m, 1 H, 2-H), 3.81 – 3.63 (m, 2 H, 1-H), 1.92 – 1.75 (m, 1 H, 3'-H), 1.75 – 1.37 (m, 6 H, 7-H to 17-H, 3'-H to 17'-H), 1.37 – 1.14 (m, 45 H, 7-H to 17-H, 3'-H to 17'-H), 0.91 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.90 – 0.83 (m, 15 H, 18-H, 18'-H, SiC($C\underline{H}_3$)$_3$), 0.10, 0.06, 0.04, 0.01 (4s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

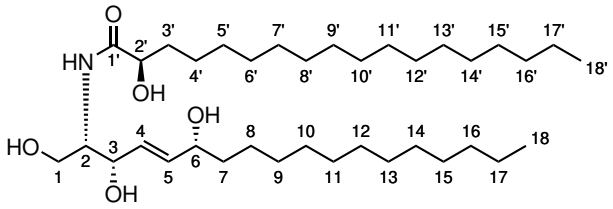
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{44}H_{91}NNaO_5Si_2$ 792.6328, found 792.6397.

IR (ATR): ν_{max} = 2953, 2923, 2854, 1653, 1464, 1253, 1083 cm^{-1}.

$[\alpha]_D^{25}$**:** +8.22° ($c = 0.6$; $CHCl_3$).

(*R*)-2-Hydroxy-*N*-((*2S,3S,6R,E*)-1,3,6-trihydroxyoctadec-4-en-2-yl)octadecanamide (130)

exp: 102
DL608



According to GP 24, the reaction of Amide **129** (7.2 mg, 8.71 µmol) with HF·pyridine (18.5 µL, 21.8 µmol) yielded, after preparative RP-TLC (H_2O/MeCN 5/95, R_f=0.5), **130** as a colorless oil (0.4 mg, 8 %).

^{1}H-NMR (600 MHz, DMSO−d_6): δ = 7.11 (d, J = 8.9 Hz, 1 H, N-H), 5.60 (d, J = 5.1 Hz, 1 H, O-H), 5.53 (dd, J = 15.6, 5.5 Hz, 1 H, 5-H), 5.47 (dd, J = 15.6, 5.8 Hz, 1 H, 4-H), 5.13 (d, J = 4.7 Hz, 1 H, O-H), 4.72 (t, J = 5.5 Hz, 1 H, O-H), 4.55 (d, J = 4.8 Hz, 1 H, O-H), 4.30 – 4.26 (m, 1 H, 3-H), 3.85 – 3.80 (m, 2 H, 6-H, 2'-H), 3.66 (dt, J = 10.6, 7.2 Hz, 1 H, 2-H), 3.42 (ddd, J = 9.9, 7.9, 6.1 Hz, 2 H, 1-H), 1.61 – 1.54

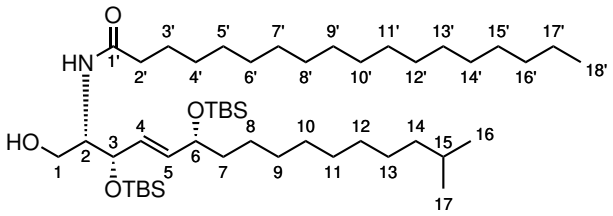
(m, 1 H, 3'-H), 1.49 – 1.41 (m, 3 H, 7-H to 17-H, 3'-H to 17'-H), 1.36 – 1.17 (m, 48 H, 7-H to 17-H, 3'-H to 17'-H), 0.97 – 0.82 (m, 6 H, 18-H, 18'-H) ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{36}H_{71}NNaO_5$ 620.5224, found 620.5225.

IR (ATR): ν_{max} = 3296, 2848, 1599, 1531, 1404, 1319, 1086 cm^{-1}.

N-((*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)stearamide (131)

exp: 103
DL518



According to GP 22, the reaction of amine **114** (40 mg, 69.4 µmol) with stearic acid (21.7 mg, 76.4 µmol), DCC (18.6 mg, 90.3 µmol) and DIPEA (13.3 µL, 76.4 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 55/45), **131** as a yellowish oil (16.2 mg, 30 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.93 (d, J = 7.5 Hz, 1 H, N-H), 5.68 (dd, J = 15.5, 5.0 Hz, 1 H, 5-H), 5.58 (dd, J = 15.3, 5.8 Hz, 1 H, 4-H), 4.39 (dd, J = 6.0, 3.1 Hz, 1 H, 3-H), 4.14 – 4.05 (m, 1 H, 6-H), 3.95 – 3.82 (m, 1 H, 2-H), 3.79 – 3.52 (m, 2 H, 1-H), 2.18 (dd, J = 9.1, 6.3 Hz, 2 H, 2'-H), 1.80 – 1.57 (m, 5 H, 7-H to 13-H, 3'-H to 17'-H), 1.56 – 1.36 (m, 3 H, 7-H to 15-H, 3'-H to 17'-H), 1.36 – 1.16 (m, 64 H, 7-H to 13-H, 3'-H to 17'-H), 1.17 – 1.11 (m, 2 H, 14-H to)-H, 0.91, 0.88 (2s, 2x 9 H, $SiC(C\underline{H}_3)_3$), 0.87 – 0.79 (m, 9 H, 16-H, 17-H, 18'-H), 0.09, 0.05, 0.03, −0.00, (4s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 174.2 (s, C-1'), 136.0 (d, C-5), 128.9 (d, C-4), 72.4 (d, C-6), 71.6 (d, C-3), 64.1 (t, C-1), 56.5 (d, C-2), 39.2 (t, C-14), 38.5 (t, C-7), 36.9 (t, C-2'), 32.1, 30.1, 29.9, 29.81, 29.78, 29.75, 29.66, 29.5, 29.4 (9t, C-8 to C-13, C-3' to C-17'), 28.1 (d, C-15), 27.6 (t, C-8 to C-13, C-3' to C-16'), 26.02, 26.00 (2q, $Si(\underline{C}H_3)_2$), 25.8, 25.4 (2 t, C-8 to C-13, C-3' to C-17'), 22.8 (q, C-16, C-17), 18.3, 18.2 (2s, $Si\underline{C}(CH_3)_3$), 14.3 (C-18'), −4.0, −4.2, −4.7, −4.9 (4q, $Si(\underline{C}H_3)_2$) ppm.

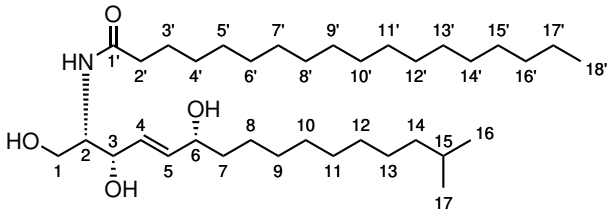
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{47}H_{97}NNaO_4Si_2$ 818.6848, found 818.6871.

IR (ATR): ν_{max} = 2951, 2924, 2853, 1652, 1507, 1083 cm^{-1}.

$[\alpha]_D^{25}$**:** -3.00° (c = 1.0; $CHCl_3$).

N-((*2S,3S,6R,E*)-1,3,6-Trihydroxy-15-methylhexadec-4-en-2-yl)stearamide (132)

exp: 104
DL538



According to GP 23, the reaction of amide **131** (13.0 mg, 16.3 µmol) with TBAF (50.0 µL, 50.0 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 0/100), **132** as a colorless solid (0.8 mg, 9 %).

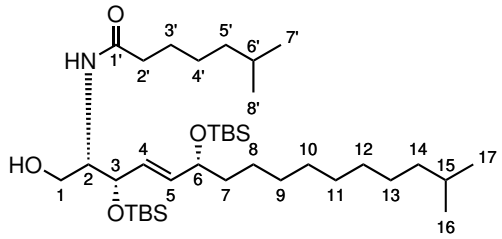
^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.14 (d, J = 8.0 Hz, 1 H, N-H), 5.80 (dd, J = 15.2, 6.0 Hz, 1 H, 5-H), 5.71 (dd, J = 15.4, 5.6 Hz, 1 H, 4-H), 4.52 – 4.44 (m, 1 H, 3-H), 4.11 (q, J = 6.3 Hz, 1 H, 6-H), 3.94 (dt, J = 7.8, 3.9 Hz, 1 H, 2-H), 3.87 (dd, J = 11.1, 4.1 Hz, 1 H, 1-H), 3.81 (dd, J = 11.1, 4.5 Hz, 1 H, 1-H), 2.27 – 2.18 (m, 2 H, 2'-H), 1.56 – 1.46 (m, 1 H, 15-H), 1.42 – 1.19 (m, 24 H, 7-H to 13-H, 3'-H to 17'-H), 1.14 (q, J = 6.8 Hz, 2 H, 14-H), 0.90 – 0.84 (m, 5 H, 16-H, 17-H, 18'-H) ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{35}H_{69}NNaO_4$ 590.5119, found 590.5097.

$[\alpha]_D^{25}$**:** -7.2° (c = 0.1; $CHCl_3$).

N-((*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)-6-methylheptanamide (133)

exp: 105
DL308

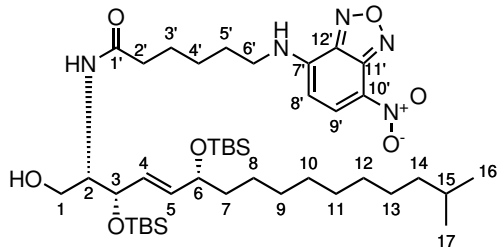


According to GP 22, the reaction of amine **114** (100 mg, 189 µmol) with carboxylic acid **63** (29.9 mg, 208 µmol) and DCC (46.7 mg, 226 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 50/50), **133** as a colorless wax (25.4 mg, 21 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.87 (d, J = 7.5 Hz, 1 H, N-H), 5.67 (dd, J = 15.5, 5.5 Hz, 1 H, 5-H), 5.56 (dd, J = 15.5, 5.4 Hz, 1 H, 4-H), 4.40 (dd, J = 5.5, 2.7 Hz, 1 H, 3-H), 4.09 (q, J = 5.8 Hz, 1 H, 6-H), 3.91 (qd, J = 6.1, 2.7 Hz, 1 H, 2-H), 3.78 – 3.54 (m, 2 H, 1-H), 2.24 – 2.13 (m, 2 H, 2'-H), 1.72 – 1.39 (m, 7 H, 7-H, 15-H, 3'-H, 6'-H), 1.37 – 1.20 (m, 17 H, 8-H to 13-H, 4'-H), 1.20 – 1.08 (m, 4 H, 14-H, 5'-H), 0.91, 0.88 (2s, 2x 9 H, $SiC(C\underline{H_3})_3$), 0.86, 0.85 (2d, J = 6.6 Hz, 2x 6 H, 16-H, 17-H, 7'-H, 8'-H), 0.09, 0.05, 0.03, 0.00 (4s, 2x 3 H, $Si(C\underline{H_3})_2$) ppm.

N-((*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)-6-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)hexanamide (134)

exp: 106
DL577



According to GP 22, the reaction of amine **114** (20.0 mg, 34.7 µmol) with 6-(7-nitrobenzofurazan-4-ylamino)hexanoic acid (12.3 mg, 41.7 µmol), HBTU (22.4 mg, 59.0 µmol) and DIPEA (15.1 µL, 86.8 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 40/60), **134** as a bright orange solid (14.1 mg, 50 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.49 (d, J = 8.6 Hz, 1 H, 8'-H), 6.16 (d, J = 8.6 Hz, 1 H, 9'-H), 5.94 (d, J = 7.6 Hz, 1 H, N-H), 5.70 (dd, J = 15.6, 5.0 Hz, 1 H, 5-H), 5.60 (dd, J = 15.8, 5.9 Hz, 1 H, 4-H), 4.40

(dd, $J = 6.0, 2.8$ Hz, 1 H, 3-H), 4.10 (q, $J = 5.7$ Hz, 1 H, 6-H), 4.01 – 3.87 (m, 1 H, 2-H), 3.80 – 3.61 (m, 2 H, 1-H), 3.61 – 3.37 (m, 2 H, 6'-H), 2.33 – 2.20 (m, 2 H, 2'-H), 1.56 – 1.48 (m, 2 H, 7-H to 13-H, 3'-H to 5'-H), 1.48 – 1.39 (m, 1 H, 15-H), 1.38 – 1.30 (m, 2 H, 7-H to 13-H, 3'-H to 5'-H), 1.30 – 1.19 (m, 16 H, 7-H to 13-H, 3'-H to 5'-H), 1.18 – 1.06 (m, 2 H, 14-H), 0.90, 0.88 (2s, 2x 9 H, $SiC(C\underline{H}_3)_3$), 0.85 (d, $J = 6.6$ Hz, 6 H, 16-H, 17-H), 0.09, 0.06, 0.03, −0.01 (4s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR: δ =1049

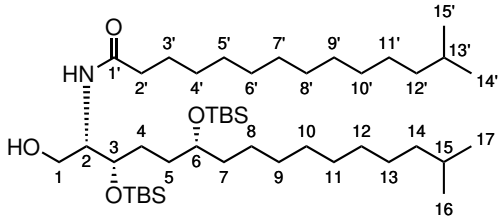
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{41}H_{75}N_5NaO_7SI_2$ 828.5097, found 828.5093.

IR (ATR): ν_{max} = 3283, 2927, 2855, 1646, 1584, 1300, 1256 cm^{-1}.

$[\alpha]_D^{25}$**:** -2.82° ($c = 1.0$; $CHCl_3$).

N-((*2S,3S,6R*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadecan-2-yl)-13-methyltetradecanamide (135)

exp: 107
DL474



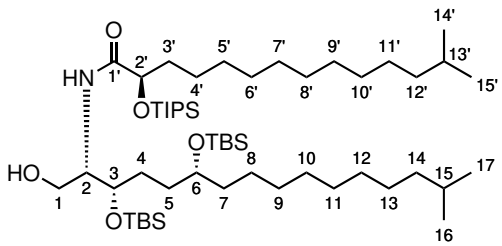
According to GP 22, the reaction of amine **117** (100 mg, 188 µmol) with carboxylic acid **34** (50.1 mg, 207 µmol) and DCC (46.5 mg, 226 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 55/45), **135** as a colorless oil (31.7 mg, 22 %).

^{1}H-NMR (300 MHz, **$CDCl_3$**)**:** δ = 5.96 (d, $J = 8.0$ Hz, 1 H, N-H), 3.98 (q, $J = 7.6, 6.9$ Hz, 1 H, 3-H), 3.88 – 3.79 (m, 1 H, 6-H), 3.72 – 3.61 (m, 1 H, 1-H), 3.61 – 3.51 (m, 2 H, 1-H, 2-H), 2.22 (t, $J = 7.5$ Hz, 2 H, 2'-H), 1.69 – 1.45 (m, 6 H, 7-H, 15-H, 13'-H), 1.45 – 1.31 (m, 4 H, 4-H, 5-H), 1.33 – 1.18 (m, 28 H, 8-H to 13-H, 3'-H to 11'-H), 1.20 – 1.10 (m, 4 H, 14-H, 12'-H), 0.90, 0.87 (2s, 2x 9 H, $SiC(C\underline{H}_3)_3$), 0.85 (d, $J = 6.6$ Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.09, 0.08, 0.02, 0.01 (4s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz, **$CDCl_3$**)**:** δ = 174.5 (s, C-1'), 72.2 (d, C-6), 71.8 (d, C-3), 65.2 (t, C-1), 54.0 (d, C-2), 39.2 (t, C-14, C-12'), 37.5 (t, C-4, C-5, C-7), 37.0 (t, C-3'), 32.8, 31.2 (2t, C-4, C-5, C-7), 30.10, 30.08, 30.05, 29.9, 29.8, 29.7, 29.5, 29.4 (8t, C-8 to C-13, C-4' to C-11'), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.1, 26.0 (2q, $SiC(\underline{C}H_3)_3$), 25.9, 25.1 (2t, C-8 to C-13, C-4' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.2, 18.1 (2s, $Si\underline{C}(CH_3)_3$), −4.0, −4.2, −4.3, −4.7 (4q, $Si(\underline{C}H_3)_2$) ppm.

(*R*)-*N*-((*2S,3S,6R*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadecan-2-yl)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamide (136)

exp: 108
DL722



According to GP 21, the reaction of amine **117** (40.0 mg, 75.2 µmol) with carboxylic acid **61** (34.3 mg, 82.7 µmol), DIPEA (19.6 µL, 113 µmol) and HBTU (34.2 mg, 90.2 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 0/100, eluting at 75/25), **136** as a colorless solid (35.0 mg, 50 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.5 Hz, 1 H, N-H), 4.38 (dd, J = 5.4, 3.4 Hz, 1 H, 2'-H), 4.07 – 3.96, 3.93 – 3.85 (2m, 2x 1 H, 3-H, 6-H), 3.74 – 3.57 (m, 2 H, 1-H, 2-H), 3.56 – 3.46 (m, 1 H, 1-H), 2.59 (dd, J = 6.9, 4.3 Hz, 1 H, 4-H, 5-H, 3'-H), 1.77 – 1.60 (m, 2 H, 4-H, 5-H, 3'-H) 1.59 – 1.45 (m, 2 H, 15-H, 13'-H), 1.40 – 1.28 (m, 2 H, 4-H, 5-H, 3'-H), 1.28 – 1.22 (m, 29 H, 7-H to 13-H, 3'-H to 11'-H), 1.18 – 1.11 (m, 4 H, 14-H, 12'-H), 1.11 – 1.03 (m, 23 H, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$), 0.88, 0.88 (2s, 2x 9 H, $SiC(C\underline{H}_3)_3$), 0.86 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.08 (s, 6 H, $Si(C\underline{H}_3)_2$), 0.03, 0.02 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 175.0 (s, C-1'), 73.6 (d, C-2'), 72.5, 72.2 (2d, C-3, C-6), 65.0 (t, C-1), 53.4 (d, C-2), 39.2 (t, C-14, C-12'), 38.1, 35.4, 33.0, 31.6 (4t, C-4, C-5, C-7, C-3'), 30.13, 30.09, 29.9, 29.8 (4t, C-8 to C-13, C-4' to C-11'), 28.1 (d, C-15, C-13'), 27.6, 27.1 (2t, C-8 to C-13, C-4' to C-11'), 26.1, 26.0 (2q, $SiC(\underline{C}H_3)_3$), 25.0, 23.3 (2t, C-8 to C-13, C-4' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.2, 18.1 (2q 2s, $Si\underline{C}(CH_3)_3$, $SiCH(\underline{C}H_3)_2$), 12.3 (d, $Si\underline{C}H(CH_3)_2$), −4.2, −4.3, −4.7 (3q, $Si(\underline{C}H_3)_2$) ppm.

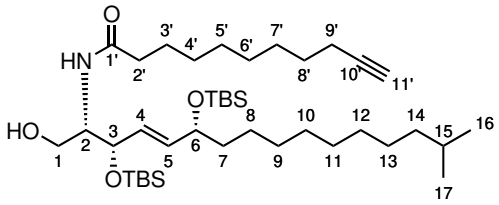
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{53}H_{114}NO_5Si_3$ 928.7999, found 928.8011.

IR (ATR) ν_{max}: 3415, 2924, 2854, 1662, 1518, 1463, 1253, 1084 cm^{-1}.

$[\alpha]_D^{25}$**:** +8.41° (c = 1.8; $CHCl_3$).

N-((*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methylhexadec-4-en-2-yl)undec-10-ynamide (137)

exp: 109
DL603



According to GP 21, the reaction of amine **114** (20.0 mg) with undec-10-ynoic acid (7.59 mg, 41.7 µmol), HBTU (22.4 mg, 59.0 µmol) and DIPEA (15.1 µL, 86.8 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 50/50), **137** as a yellowish oil (11.2 mg, 46 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.93 (d, J = 7.4 Hz, 1 H, N-H), 5.68 (dd, J = 15.5, 5.3 Hz, 1 H, 5-H), 5.62 – 5.54 (m, 1 H, 4-H), 4.39 (dd, J = 6.1, 3.0 Hz, 1 H, 3-H), 4.09 (q, J = 5.8 Hz, 1 H, 6-H), 3.88 (dt, J = 13.1, 4.8 Hz, 1 H, 2-H), 3.71 (dd, J = 10.9, 6.1 Hz, 1 H, 1-H), 3.63 (dd, J = 10.9, 5.5 Hz, 1 H, 1-H), 2.18 (qd, J = 7.3, 2.3 Hz, 4 H, 2'-H, 9'-H), 1.93 (t, J = 2.7 Hz, 1 H, 11'-H), 1.68 – 1.55 (m, 2 H, 7-H to 13-H, 3'-H to 8'-H), 1.56 – 1.46 (m, 3 H, 7-H to 15-H, 3'-H to 8'-H), 1.36 – 1.21 (m, 20 H, 7-H to 13-H, 3'-H to 8'-H), 1.16 – 1.12 (m, 2 H, 14-H), 0.91, 0.88 (2s, 2x 9 H, $SiC(C\underline{H}_3)_3$), 0.86 (d, J = 6.6 Hz, 6 H, 16-H, 17-H), 0.09, 0.06, 0.03, −0.00 (4s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 174.2 (s, C-1'), 136.0 (d, C-5), 128.9 (d, C-4), 84.8 (d, C-11'), 72.3 (d, C-6), 71.6 (d, C-3), 68.3 (s, C-10'), 64.0 (t, C-1), 56.5 (d, C-2), 39.2 (t, C-14), 38.5 (t, C-7), 36.9 (t, C-8'), 30.1, 29.84, 29.80, 29.77, 29.74, 29.4, 29.1, 28.8, 28.6 (9t, C-7 to C-13, C-3' to C-7'), 28.1 (d, C-15), 27.6 (t, C-7 to C-13, C-3' to C-7'), 26.0, 25.9 (2q, $SiC(\underline{C}H_3)_3$), 25.4 (t, C-7 to C-13, C-3' to C-7'), 22.8 (q, C-16, C-17), 18.5, 18.3 (2s, $Si\underline{C}(CH_3)_3$), 18.2 (t, C-9'), −4.0, −4.2, −4.7, −4.9 (4q, $Si(\underline{C}H_3)_2$) ppm.

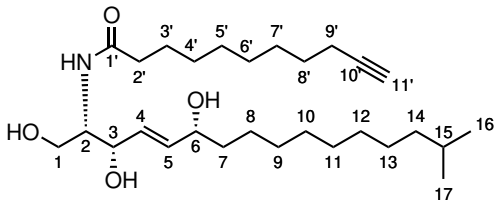
HRMS (ESI-TOF): calculated for $[M - OTBS]^+$ $C_{34}H_{64}NO_3Si$ 562.4650, found 562.4648.

IR (ATR): ν_{max} = 2952, 2926, 2855, 1652, 1463, 1253, 1218 cm^{-1}.

$[\alpha]_D^{25}$**:** -3.25° ($c = 1.1$; $CHCl_3$).

N-((*2S,3S,6R,E*)-1,3,6-Trihydroxy-15-methylhexadec-4-en-2-yl)undec-10-ynamide (138)

exp: 110
DL540



According to GP 23, the reaction of amide **137** (10.0 mg, 14.4 µmol) with TBAF (50.0 µL, 50.0 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 0/100, eluting at 0/100), **138** as a colorless solid (0.6 mg, 9 %).

^{1}H-NMR (600 MHz**, $CDCl_3$):** δ = 6.16 (d, J = 8.1 Hz, 1 H, N-H), 5.80 (dd, J = 15.5, 6.0 Hz, 1 H, 5-H), 5.71 (dd, J = 15.6, 5.8 Hz, 1 H, 4-H), 4.48 (dd, J = 5.7, 3.1 Hz, 1 H, 3-H), 4.18 – 4.06 (m, 1 H, 6-H), 3.94 (dt, J = 7.8, 4.0 Hz, 1 H, 2-H), 3.86 (dd, J = 11.1, 4.1 Hz, 1 H, 1-H), 3.81 (dd, J = 11.1, 4.5 Hz, 1 H, 1-H), 2.22 (t, J = 7.7 Hz, 2 H, 2'-H), 2.18 (td, J = 7.1, 2.4 Hz, 2 H, 9'-H), 1.94 (t, J = 2.5 Hz, 1 H, 11'-H), 1.51 (qd, J = 10.9, 9.2, 5.0 Hz, 6 H, 7-H to 13-H, 15-H, 3'-H to 8'-H), 1.38 (dt, J = 12.0, 6.6 Hz, 4 H, 7-H to 13-H, 3'-H to 8'-H), 1.35 – 1.22 (m, 26 H, 7-H to 13-H, 3'-H to 8'-H), 1.18 – 1.12 (m, 2 H, 14-H), 0.86 (d, J = 6.7 Hz, 6 H, 16-H, 17-H) ppm.

^{13}C-NMR (151 MHz**, $CDCl_3$):** δ = 174.5 (s, C-1'), 135.5 (d, C-5), 123.8 (d, C-4), 84.9 (d, C-11'), 82.2 (d, C-11'), 72.7 (d, C-3) 72.1 (d, C-6), 68.3 (s, C-10'), 64.2 (t, C-1), 54.5 (d, C-2), 39.2 (t, C-14), 37.3 (t, C-7), 36.7 (t, C-8'), 32.1, 30.1, 29.9, 29.8, 29.5, 29.3, 29.3, 29.09, 29.05, 28.8, 28.6 (11t, C-8 to C-13, C-2' to C-7'), 28.1 (d, C-15), 27.6 (t, C-8 to C-13, C-2' to C-7'), 22.8 (q, C-16, C-17), 18.5 (t, C-9') ppm.

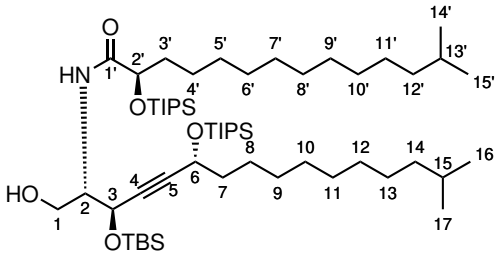
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{28}H_{51}NNaO_4$ 488.3710, found 488.3693.

IR (ATR) ν_{max}: 2958, 2923, 2853, 1636, 1085, 1014 cm^{-1}.

$[\alpha]_D^{25}$**:** -17.9° ($c = 0.1$; $CHCl_3$).

(*R*)-*N*-((*2S,3R,6R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yn-2-yl)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamide (139)

exp: 111
DL746



According to GP 21, the reaction of amine **119** (350 mg, 614 µmol) with carboxylic acid **61** (382 mg, 921 µmol), HBTU (373 mg, 982 µmol) and DIPEA (214 µL, 1.23 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 66/33), **139** as a colorless oil (420 mg, 71 %).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.3 Hz, 1 H, N-H), 4.70 – 4.60 (m, 1 H, 3-H), 4.49 (t, J = 6.1 Hz, 6 H, 6-H), 4.36 (d, J = 4.6 Hz, 1 H, 2'-H), 4.31 – 4.26 (m, 1 H, 1-H), 4.04 – 4.00 (m, 1 H, 2-H), 3.62 – 3.55 (m, 1 H, 1-H), 3.04 (d, J = 10.4 Hz, 1 H, O-H), 1.88 (tt, J = 12.5, 4.0 Hz, 1 H, 3'-H), 1.73 – 1.59 (m, 3 H, 7-H, 3'-H), 1.51 (hept, J = 6.5 Hz, 2 H, 15-H, 13'-H), 1.47 – 1.37 (m, 2 H, 8-H to 13-H, 4'-H to 11'-H), 1.37 – 1.17 (m, 30 H, 8-H to 13-H, 4'-H to 11'-H), 1.17 – 1.03 (m, 57 H, 14-H, 12'-H, SiCH($C\underline{H}_3$)$_2$, SiC$\underline{H}$(CH_3)$_2$), 0.89 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.7 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.17, 0.10 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 174.2 (s, C-1'), 89.4 (s, C-5), 81.7 (s, C-4), 73.7 (d, C-2'), 66.9 (d, C-3), 63.2 (d, C-6), 63.1 (t, C-1), 54.0 (d, C-2), 39.2 (t, C-14, C-12'), 39.0 (t, C-7) 35.7 (t, C-3'), 30.1, 29.87, 29.84, 29.81, 29.78, 29.76, 29.64 (7t, C-8 to C-13, C-4' to C-11'), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 25.9 (q, SiC($\underline{C}H_3$)$_3$), 23.7 (t, C-8 to C-13, C-4' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.2, 18.1 (2q, SiCH($\underline{C}H_3$)$_2$), 17.8 (s, Si$\underline{C}$(CH_3)$_3$), 12.38, 12.36 (2d, Si$\underline{C}$H(CH_3)$_2$), −4.4, −5.2 (2q, Si($\underline{C}H_3$)$_2$) ppm.

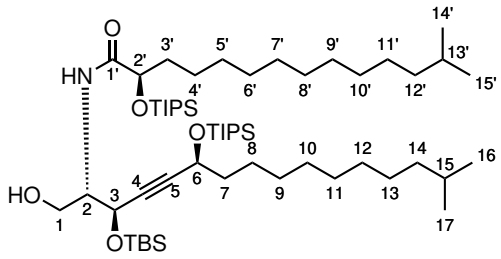
HRMS (ESI-TOF): calculated for $[M + NH_4]^+$ $C_{56}H_{119}N_2O_5Si_3$ 983.8421, found 983.8398.

IR (ATR) ν_{max}: 3397, 2925, 2864, 1668, 1519, 1463, 1091, 1064 cm^{-1}.

$[\alpha]_D^{25}$**:** +2.77° (c = 1.0; $CHCl_3$).

(*R*)-*N*-((*2S*,*3R*,*6S*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yn-2-yl)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamide (140)

exp: 112
DL738



According to GP 21, the reaction of amine **118** (60 mg, 105 µmol) with carboxylic acid **61** (65.5 mg, 158 µmol), HBTU (63.9 mg, 168 µmol) and DIPEA (36.7 µL, 211 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 92/8), **140** as a colorless oil (48 mg, 47 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.3 Hz, 1 H, N-H), 4.64 (s, 1 H, 3-H), 4.50 (t, J = 5.8 Hz, 1 H, 6-H), 4.38 – 4.34 (m, 1 H, 2'-H), 4.30 (d, J = 11.2 Hz, 1 H, 1-H), 4.02 (dd, J = 8.0, 2.9 Hz, 1 H, 2-H), 3.59 (td, J = 11.2, 3.6 Hz, 1 H, 1-H), 3.01 (d, J = 10.3 Hz, 1 H, O-H), 1.96 – 1.84 (m, 1 H, 3'-H), 1.78 – 1.62 (m, 4 H, 7-H to 13-H, 3'-H to 11'-H) 1.51 (tt, J = 11.3, 5.7 Hz, 3 H, 7-H to 13-H, 14-H, 3'-H to 11'-H, 13'-H), 1.33 – 1.19 (m, 33 H, 7-H to 13-H, 3'-H to 11'-H), 1.18 – 1.01 (m, 63 H, 14-H, 12'-H, SiC$\underline{H}$(CH_3)$_2$, SiCH($C\underline{H}_3$)$_2$), 0.90 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.17, 0.11 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 174.1 (s, C-1'), 89.4 (s, C-5), 81.7 (s, C-4), 73.8 (d, C-2'), 67.1 (d, C-3), 63.2 (d, C-6), 63.0 (t, C-1), 54.0 (C-2), 39.2 (t, C-14, C-12'), 39.0 (t, C-7), 35.8 (t, C-3'), 30.1, 29.9, 29.85, 29.79, 29.7 (5t, C-8 to C-13, C-4' to C-11'), 28.1 (d, C-15, C-13'), 27.6, 27.1 (2t, C-8 to C-13,

C-4' to C-11'), 25.9 (q, SiC($\underline{C}H_3)_3$), 23.8 (C-t, C-7), 22.8 (q, C-16, C-17, C-14', C-15'), 18.2, 18.1 (2q, SiCH($\underline{C}H_3)_2$), 17.9 (s, Si$\underline{C}(CH_3)_3$), 12.4 (d, Si$\underline{C}H(CH_3)_2$), −4.4, −5.2 (2q, Si($\underline{C}H_3)_2$) ppm.

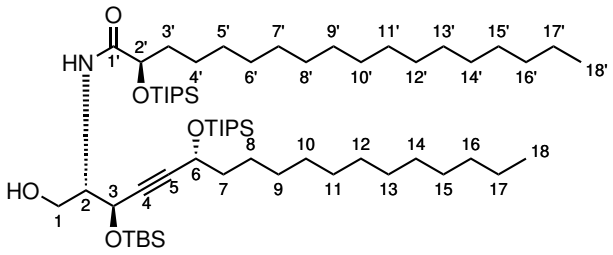
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{56}H_{115}O_5NNaSi_3$ 988.7975, found 988.7939.

IR (ATR): ν_{max} = 3406, 2925, 2864, 1661, 1518, 1463, 1254, 1090, 1065 cm^{-1}.

$[\alpha]_D^{25}$**:** -3.85° ($c = 1.0$; $CHCl_3$).

(*R*)-*N*-((*2S,3R,6R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-6-((triisopropylsilyl)oxy)octadec-4-yn-2-yl)-2-((triisopropylsilyl)oxy)octadecanamide (141)

exp: 113
DL770



According to GP 21, the reaction of amine **123** (100 mg, 171 µmol) with carboxylic acid **59** (86.0 mg, 188 µmol), HBTU (84.4 mg, 223 µmol) and DIPEA (59.6 µL, 342 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 0/100, eluting at 66/33), **141** as a colorless oil (67.8 mg, 39 %).

^{1}**H-NMR** (500 MHz**, $CDCl_3$):** δ = 7.61 (d, J = 8.3 Hz, 1 H, N-H), 4.67 – 4.59 (m, 1 H, 3-H), 4.49 (t, J = 6.1 Hz, 1 H, 6-H), 4.36 (dd, J = 5.6, 3.7 Hz, 1 H, 2'-H), 4.28 (dd, J = 11.7, 2.8 Hz, 1 H, 1-H), 4.02 (dq, J = 9.2, 3.2 Hz,1 H, 2-H), 3.59 (dd, J = 11.7, 3.8 Hz, 1 H, 1-H), 1.88 (tt, J = 12.0, 3.9 Hz, 1 H, 3'-H), 1.74 – 1.62 (m, 3 H, 7-H, 3'-H), 1.55 – 1.36 (m, 4 H, 8-H to 17-H, 4'-H to 17'-H), 1.34 – 1.23 (m, 59 H, 8-H to 17-H, 4'-H to 17'-H), 1.18 – 0.99 (m, 55 H, SiCH($\underline{CH_3}$)$_2$, SiC$\underline{H}(CH_3)_2$), 0.90 (s, 9 H, SiC($\underline{CH_3}$)$_3$), 0.88 (t, J = 6.5 Hz, 6 H, 18-H, 18'-H), 0.17, 0.11 (2s, 2x 3 H, Si($\underline{CH_3}$)$_2$) ppm.

^{13}**C-NMR** (126 MHz**, $CDCl_3$):** δ = 174.2 (s, C-1'), 89.5 (s, C-5), 81.7 (s, C-4), 73.7 (d, C-2'), 66.9 (d, C-3), 63.2 (d, C-6), 63.1 (t, C-1), 54.0 (d, C-2), 39.0 (t, C-7), 35.7 (t, C-3'), 32.1, 29.89, 29.86, 29.81, 29.76, 29.72, 29.65, 29.6, 29.52 (9t, C-8 to C-17, C-4' to C-17'), 25.9 (q, SiC($\underline{C}H_3)_3$), 25.1, 23.7, 22.8 (3t, C-8 to C-17, C-4' to C-17'), 18.2, 18.1 (2q, SiCH($\underline{C}H_3)_2$), 17.9 (s, Si($\underline{C}H_3)_2$), 14.3 (q, C-18, C-18'), 12.5, 12.4 (2d, Si$\underline{C}H(CH_3)_2$), −4.4, −5.2 (2q, Si($\underline{C}H_3)_2$) ppm.

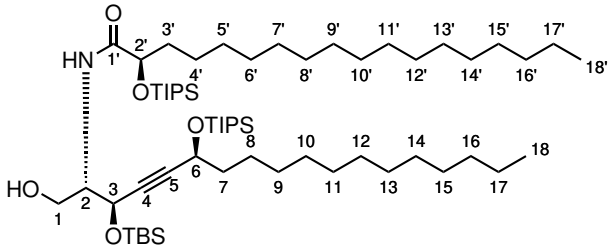
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{60}H_{123}NNaO_5Si_3$ 1044.8601, found 1044.8621.

IR (ATR) ν_{max}: 2923, 2854, 1664, 1518, 1463, 1252, 1093, 1065 cm^{-1}.

$[\alpha]_D^{25}$**:** +3.35° ($c = 1.0$; $CHCl_3$).

(*R*)-*N*-((*2S,3R,6S*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-6-((triisopropylsilyl)oxy)octadec-4-yn-2-yl)-2-((triisopropylsilyl)oxy)octadecanamide (142)

exp: 114
DL771



According to GP 21, the reaction of amine **122** (100 mg, 171 µmol) with carboxylic acid **59** (86.0 mg, 188 µmol), HBTU (104 mg, 274 µmol) and DIPEA (59.6 µL, 342 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 0/100, eluting at 66/33), **142** as a colorless oil (104 mg, 59 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.3 Hz, 1 H, N-H), 4.67 – 4.59 (m, 1 H, 3-H), 4.55 – 4.44 (m, 1 H, 6-H), 4.36 (dd, J = 5.5, 3.8 Hz, 1 H, 2'-H), 4.30 (dd, J = 11.8, 2.7 Hz, 1 H, 1-H), 4.02 (dt, J = 8.4, 3.1 Hz, 1 H, 2-H), 3.59 (dd, J = 11.7, 3.8 Hz, 1 H, 1-H), 1.89 (tt, J = 12.2, 3.9 Hz, 1 H, 3'-H), 1.73 – 1.61 (m, 3 H, 7-H, 3'-H), 1.54 – 1.36 (m, 4 H, 8-H to 17-H, 4'-H to 17'-H), 1.34 – 1.23 (m, 59 H, 8-H to 17-H, 4'-H to 17'-H), 1.17 – 1.01 (m, 55 H, SiCH($C\underline{H}_3$)$_2$, Si$C\underline{H}$(CH_3)$_2$), 0.89 (s, 9 H, SiC($C\underline{H}_3$)$_3$), 0.88 (t, J = 6.5 Hz, 6 H, 18-H, 18'-H), 0.17, 0.11 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 174.2 (s, C-1'), 89.4 (s, C-5), 81.6 (s, C-4), 73.8 (d, C-2'), 67.1 (d, C-3), 63.2 (d, C-6), 63.0 (t, C-1), 54.0 (d, C-2), 39.0 (t, C-7), 35.7 (t, C-3'), 32.1, 29.89, 29.86, 29.81, 29.76, 29.72, 29.65, 29.6, 29.55, 29.52 (10t, C-8 to C-17, C-4' to C-17'), 25.9 (q, SiC($C\underline{H}_3$)$_3$), 25.1, 23.7, 22.8 (3t, C-8 to C-17, C-4' to C-17'), 18.2, 18.1 (2q, SiCH($C\underline{H}_3$)$_2$), 17.9 (s, Si($C\underline{H}_3$)$_2$), 14.3 (q, C-18, C-18'), 12.5, 12.4 (2d, Si$C\underline{H}$(CH_3)$_2$), −4.4, −5.2 (2q, Si($C\underline{H}_3$)$_2$) ppm.

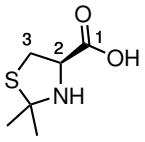
IR (ATR) ν_{max}: 2924, 2854, 1661, 1514, 1463, 1253, 1092, 1064 cm^{-1}.

$[\alpha]_D^{25}$**:** -8.27° (c = 1.0; $CHCl_3$).

4.5 Investigation of the cysteine strategy

(*R*)-4-Carboxy-2,2-dimethylthiazolidin-3-ium chloride (SI-19)

exp: 115
DL511



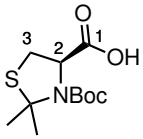
2,2-Dimethoxypropane (124 mL, 1.34 mol) was added to a suspension of L-cysteine hydrochloride (26.4 g, 168 mmol) in acetone (560 mL) and the reaction refluxed for 16 h. The suspension was filtered hot, washed with acetone and the filtrate dried *in vacuo* to yield **SI-19** as colorless crystals (24.3 g). The mother liquor's volume was reduced *in vacuo*, the remaining solid suspended in acetone, filtered, washed with pentane and dried *in vacuo* to yield another batch of colorless crystals (3.50 g, sum: 84 %).

^{1}H-NMR (300 MHz, D_2O): δ = 4.86 (dd, J = 7.8, 1.5 Hz, 1 H, 2-H), 3.64 (dd, J = 12.3, 8.1 Hz, 1 H, 3-H), 3.51 (dd, J = 12.2, 8.0 Hz, 1 H, 3-H), 1.80, 1.78 (2s, 2x 3 H, C($C\underline{H}_3$)$_2$) ppm.

The analytical data is consistent with literature reports.[126]

(*R*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethylthiazolidine-4-carboxylic acid (144)

exp: 116
DL516



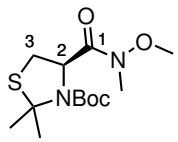
Di-*tert*-butyl dicarbonate (28.4 g, 130 mmol) was added to a solution of thiazolidine **SI-19** (24.3 g, 123 mmol) in pyridine (112 mL) at −20 °C and the mixture was stirred at r.t. for 6 h. Toluene (200 mL) was added and the aqueous phase extracted with ice cold NaOH (2 M, 150 mL, 3x). The combined aqueous phase was washed with toluene and cyclohexane and acidified using solid citric acid while cooling with an ice bath. The aqueous phase was extracted with CH_2Cl_2, the combined organic phase from acidic extraction was washed with brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo*. The remaining yellow oil was recrystallized from hot cyclohexane to yield **144** as a colorless powder (19.2 g, 60 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.04 – 4.63 (m, 1 H, 2-H), 3.44 – 3.10 (m, 2 H, 3-H), 1.95 – 1.70 (m, 6 H, C(C$\underline{H_3}$)$_2$), 1.59 – 1.30 (m, 9 H, Boc–C(C$\underline{H_3}$)$_3$) ppm.

The analytical data is consistent with literature reports.[126]

tert-Butyl (*R*)-4-(methoxy(methyl)carbamoyl)-2,2-dimethylthiazolidine-3-carboxylate (SI-20)

exp: 117
DL523



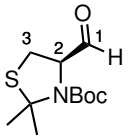
N,*O*-Dimethylhydroxylamine hydrochloride (7.80 g, 80.0 mmol) and DIPEA (12.7 mL, 72.7 mmol) were added to a solution of carboxylic acid **144** (19.0 g, 72.7 mmol) in EtOAc (240 mL) at 0 °C. A solution of DCC (16.5 g, 80.0 mmol) in EtOAc (106 mL) was added to this colorless suspension dropwise over 45 min. The mixture was stirred at 0 °C for 2 h and at r.t. for 24 h. The suspension was filtered, the volatiles removed *in vacuo* and the residue taken up in cyclohexane, the newly formed precipitate filtered hot and the volatiles removed *in vacuo*. The solid was recrystallized from MeOH/H_2O (1/1) to yield **SI-20** as a colorless solid (19.3 g), the mother liquor was purified *via* flash chromatography (cyclohexane/EtOAc 98/2 → 0/100, eluting at 70/30) to yield further colorless solid (926 mg, 91 % combined yield).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.26 – 4.89 (m, 1 H, 2-H), 3.77, 3.73 (2s, together 3 H, OC$\underline{H_3}$), 3.32 (dd, J = 12.2, 7.3 Hz, 1 H, 3-H), 3.21 (s, 3 H, NC$\underline{H_3}$), 2.97 (dd, J = 12.2, 3.9 Hz, 1 H, 3-H), 1.89, 1.82, 1.78 (3s, together 6 H, C(C$\underline{H_3}$)$_2$), 1.46, 1.40 (2s, together 9 H, Boc–C(C$\underline{H_3}$)$_3$) ppm.

The analytical data is consistent with literature reports.[126]

tert-Butyl (*R*)-4-formyl-2,2-dimethylthiazolidine-3-carboxylate (145)

exp: 118
DL521



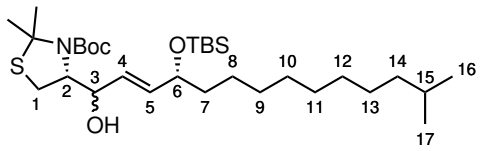
$LiAlH_4$ (83.9 mg, 2.21 mmol) was added portionwise to a solution of Weinreb amide **SI-20** (1.02 g, 3.35 mmol) in Et_2O (11.2 mL) at 0 °C and the reaction stirred for 1 h. Further $LiAlH_4$ (83.9 mg, 2.21 mmol) was added and the mixture stirred at 0 °C for 2 h. $NaHSO_4$ (300 mg) in H_2O (1 mL) was slowly added, resulting in gas formation, and the suspension stirred at 0 °C for 1 h. The precipitate was filtered off, washed with TBME and the combined organic phase washed with HCl (0.1 M), $NaHCO_3$ solution and brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo*. The residue was purified with Kugelrohr-distillation (170 °C, 0.1 – 0.3 hPa) to yield **145** as a yellowish liquid (586 mg, 71 %).

^{1}H-NMR (300 MHz**, $CDCl_3$):** δ = 9.55 (s, 1 H, 1-H), 4.80 – 4.46 (m, 1 H, 2-H), 3.22 – 3.02 (m, 2 H, 3-H), 1.90 – 1.71 (m, 6 H, $C(C\underline{H_3})_2$), 1.52 – 1.37 (m, 9 H, Boc–$C(C\underline{H_3})_3$) ppm.

The analytical data is consistent with literature reports.[126]

tert-Butyl (*R*)-4-((*4R,E*)-4-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-13-methyltetradec-2-en-1-yl)-2,2-dimethylthiazolidine-3-carboxylate (146)

exp: 119
DL522



According to GP 17, the reaction of aldehyde **145** (100 mg, 407 µmol) and alkyne **79** (146 mg) yielded, after flash chromatography (cyclohexane/EtOAc100/0 → 50/50, eluting at 89/11) **146** as a yellowish oil (82.2 mg, 35 %, 55/45 diasteromeric mixture).

^{1}H-NMR (600 MHz**, $CDCl_3$):** δ = 5.81 (ddd, J = 15.4, 5.5, 1.5 Hz), 5.72 (dd, J = 15.4, 5.8 Hz, together 1 H, 5-H), 5.67 – 5.56 (m, 1 H, 4-H), 4.59 (q, J = 4.8 Hz), 4.43 – 4.31 (m, together 2 H, 2-H, 3-H), 4.16 – 4.06 (m, 1 H, 6-H), 3.09 (td, J = 12.2, 6.1 Hz, 1 H, 1-H), 2.93 (d, J = 12.1 Hz), 2.66 (d, J = 12.1 Hz, together 1 H, 1-H), 1.81 – 1.76 (m, 6 H, $C(C\underline{H_3})_2$), 1.49, 1.48 (2s, together 10 H, 7-H, Boc–$C(C\underline{H_3})_3$), 1.37 – 1.18 (m, 13 H, 8-H to 13-H, 15-H), 1.17 – 1.03 (m, 2 H, 14-H), 0.88 (s, 9 H, $SiC(\underline{C}H_3)_3$), 0.85 (d, J = 6.4 Hz, 6 H, 16-H, 17-H), 0.04, 0.03, 0.02, 0.01 (4s, together 12 H, $Si(C\underline{H_3})_2$) ppm.

^{13}C-NMR (151 MHz**, $CDCl_3$):** δ = 156.3, 153.1 (2s, Boc–CO), 137.4, 136.0 (2d, C-5), 129.7, 128.6 (2s, C-4), 81.7, 80.9 (2s, Boc–$\underline{C}(CH_3)_3$), 76.1, 74.1 (2d, C-3), 72.8, 72.7 (2d, C-6), 71.1, 70.5 (2s, $\underline{C}(CH_3)_2$), 68.6, 67.7 (2d, C-2), 39.2 (t, C-14), 38.4, 38.3 (2t, C-7), 30.1, 30.0, 29.78, 29.75, 29.7, 29.6 (6t, C-8 to C-13), 29.4, 28.9 (2q, $C(\underline{C}H_3)_2$), 28.61, 28.56 (2q, Boc–$C(\underline{C}H_3)_3$), 28.1 (d, C-15), 26.0 (q, $SiC(\underline{C}H_3)_3$), 25.4 (t, C-8 to C-13), 22.8 (q, C-16, C-17), 18.39, 18.36 (2s, $Si\underline{C}(CH_3)_3$), −4.08, −4.10, −4.61, −4.63 (4q, $Si(\underline{C}H_3)_2$) ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{31}H_{61}NO_4NNaSSi$ 594.3983, found 594.3989.

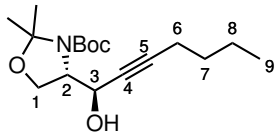
IR (ATR): ν_{max} = 2953, 2926, 2855, 1697, 1456, 1362, 1168 cm^{-1}.

$[\alpha]_D^{25}$**:** -15.2° (c = 1.0; $CHCl_3$).

4.6 Investigation of the thioligation strategy

tert-Butyl (*S*)-4-((*R*)-1-hydroxyhept-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (148)

exp: 120
DL639



n-BuLi was added dropwise to a solution of hex-1-yne (2.15 g, 26.2 mmol) in THF (52.3 mL) at −78 °C and the yellow mixture stirred for 2 h. A solution of HMPA (15.6 g, 87.2 mmol) in THF (43.6 mL) was added at −78 °C leading to a deep-orange color change. The mixture was stirred for 60 min, then a solution of Garner's aldehyde **11** (5.00 g, 21.8 mmol) in THF (43.6 mL) was added dropwise at −78 °C and the mixture stirred for 30 min. The cooling bath was removed, the reaction was stirred at r.t. for 1 h and then cooled to 0 °C. Sat. NH_4Cl solution was added, the aqueous phase extracted with TBME, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 90/10) to yield **148** as a yellowish oil (3.22 g, 47 %).

^{1}H-NMR (300 MHz, **C_6D_6**)**:** δ = 4.67 (s, 1 H, 3-H), 4.22 – 3.55 (m, 3 H, 1-H, 2-H), 2.02 (td, J = 6.8, 1.8 Hz, 2 H, 6-H), 1.73 – 1.56 (br. s, 3 H, C($\underline{CH_3}$)$_2$), 1.53 – 1.42 (br. s, 3 H, C($\underline{CH_3}$)$_2$) 1.42 – 1.21 (m, 13 H, 7-H, 8-H, Boc−C($\underline{CH_3}$)$_3$), 0.77 (t, J = 7.0 Hz, 3 H, 9-H) ppm.

^{13}C-NMR (75 MHz, **C_6D_6**)**:** δ = 153.9 (s, Boc−CO), 95.1 (s, $\underline{C}$(CH$_3$)$_2$), 86.1 (s, C-5), 80.4 (s, Boc−$\underline{C}$(CH$_3$)$_3$), 79.8 (s, C-4), 65.2 (t, C-1), 63.8, 63.4 (2d, C-2, C-3), 31.1 (t, C-7), 28.5 (q, Boc−C($\underline{C}$H$_3$)$_3$), 26.2 (q, C($\underline{C}$H$_3$)$_2$), 22.2 (t, C-8), 18.7 (t, C-6), 13.7 (q, C-9) ppm.

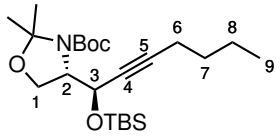
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{17}H_{30}NO_4$ 312.2169, found 312.2160.

IR (ATR): ν_{max} = 2933, 2872, 1692, 1390, 1365, 1249, 1065 cm^{-1}.

$[\alpha]_D^{25}$**:** -58.8° (c = 1.0; $CHCl_3$).

tert-Butyl (*S*)-4-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)hept-2-yn-1-yl)-2,2-dimethyloxazolidine-3-carboxylate (149)

exp: 121
DL642



According to GP 15, the reaction of oxazolidine **148** (1.50 g, 4.82 mmol) with 2,6-lutidine (1.12 mL, 9.63 mmol), 4-DMAP (58.9 mg, 481 µmol) and TBSOTf (1.22 mL, 5.30 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 90/10, eluting at 90/10), **149** as a colorless oil (1.24 g, 60 %).

^{1}H-NMR (300 MHz, **C_6D_6**)**:** δ = 4.42 (dd, J = 8.6, 4.3 Hz, 1 H, 3-H), 4.27 – 4.08 (m, 1 H, 1-H), 4.08 – 3.87 (m, 2 H, 1-H, 2-H), 1.97 (td, J = 6.7, 2.0 Hz, 2 H, 6-H), 1.88 – 1.48 (m, 6 H, C($\underline{CH_3}$)$_2$), 1.43 (s, 10 H, Boc−C($\underline{CH_3}$)$_3$), 1.35 – 1.20 (m, 4 H, 7-H, 8-H), 1.03 (s, 9 H, SiC($\underline{CH_3}$)$_3$), 0.78 (t, J = 7.0 Hz, 3 H, 9-H), 0.25, 0.20 (2s, 2x 3 H, Si($\underline{CH_3}$)$_2$) ppm.

^{13}C-NMR (75 MHz, C_6D_6): δ = 152.5 (s, Boc–CO), 94.7 (s, $\underline{C}(CH_3)_2$), 86.3 (s, C-5), 80.6 (s, Boc–$\underline{C}(CH_3)_3$), 79.5 (s, C-4), 64.1 (t, C-1), 63.1 (d, C-2), 61.5 (d, C-3), 31.0 (t, C-7), 28.6 (q, Boc–C($\underline{C}H_3)_3$), 26.3 (q, SiC($\underline{C}H_3)_3$), 26.0 (q, C($\underline{C}H_3)_2$), 22.2 (t, C-8), 18.6 (t, s, C-6, Si$\underline{C}(CH_3)_3$), 13.6 (q, C-9), −2.7, −4.3 (2q, Si($\underline{C}H_3)_2$) ppm.

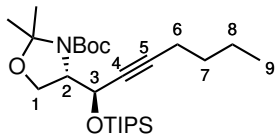
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{23}H_{44}O_4NSi$ 426.3034, found 426.3027.

IR (ATR): ν_{max} = 2958, 2931, 2858, 1692, 1462, 1390, 1364, 1252, 1172, 1069 cm^{-1}.

$[\alpha]_D^{25}$**:** -61.9° (c = 2.0; $CHCl_3$).

tert-Butyl (*S*)-2,2-dimethyl-4-((*R*)-1-((triisopropylsilyl)oxy)hept-2-yn-1-yl)oxazolidine-3-carboxylate (150)

exp: 122
DL654



According to GP 15, the reaction of oxazolidine **148** (530 mg, 1.70 mmol) with 2,6-lutidine (395 µL, 3.40 mmol), 4-DMAP (20.8 mg, 170 µmol) and TIPSOTf (503 µL, 1.87 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 70/30, eluting at 85/15), **150** as a colorless oil (571 mg, 72 %).

^{1}H-NMR (300 MHz, C_6D_6): δ = 5.60 – 5.38, 5.24 – 5.06 (2m, together 1 H, 3-H), 4.48 (dt, J = 7.8, 3.9 Hz, 1 H, 1-H), 4.21 (dt, J = 7.2, 3.7 Hz, 1 H, 2-H), 4.08 – 3.89 (m, 1 H, 1-H), 2.08 – 1.90 (m, 2 H, 6-H), 1.69, 1.63 (2s, together 3 H, C($C\underline{H}_3)_2$) 1.53 – 1.36 (m, 12 H, C($C\underline{H}_3)_2$, Boc–C($C\underline{H}_3)_3$), 1.35 – 1.12 (m, 26 H, 7-H, 8-H, SiCH($C\underline{H}_3)_2$, Si$\underline{C}H(CH_3)_2$), 0.78 (t, J = 7.1 Hz, 3 H, 9-H)ppm.

^{13}C-NMR (75 MHz, C_6D_6): δ = 152.8 (s, Boc–CO), 94.8 (s, $\underline{C}(CH_3)_2$), 86.4 (s, C-5), 80.8 (s, C-4), 79.7 (s, Boc–$\underline{C}(CH_3)_3$), 64.1 (t, C-1) 63.6 (d, C-2), 62.0 (d, C-3), 30.9 (t, C-7), 28.6 (q, Boc–C($\underline{C}H_3)_3$), 26.9, 25.7 (2q, C($\underline{C}H_3)_2$) 22.2 (t, C-8), 18.7 (t, C-6), 18.5, (q, SiCH($\underline{C}H_3)_2$), 13.6 (q, C-9), 13.1, (d, Si$\underline{C}H(CH_3)_2$) ppm.

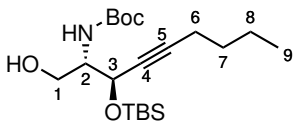
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{26}H_{50}O_4NSi$ 468.3504, found 468.3498.

IR (ATR): ν_{max} = 2958, 2939, 2866, 1692, 1463, 1389, 1364, 1248, 1172, 1093, 1069 cm^{-1}.

$[\alpha]_D^{25}$**:** -52.7° (c = 0.8; $CHCl_3$).

tert-Butyl ((*2S,3R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxynon-4-yn-2-yl)carbamate (151)

exp: 123
DL648



According to GP 20, the reaction of oxazolidine **149** (720 mg, 1.69 mmol) with PPTS (63.8 mg, 253 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 40/60, eluting at 80/20), **151** as a colorless oil (190 mg, 29 %).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 5.37 – 5.30 (m, 1 H, N-H), 4.69 (s, 1 H, 3-H), 4.31 – 4.24 (m, 1 H, 2-H), 3.65 (dd, J = 11.5, 4.1 Hz, 1 H, 1-H), 3.63 – 3.56 (m, 1 H, 1-H), 2.19 (td, J = 6.9, 2.1 Hz, 2 H, 6-H), 1.53 – 1.33 (m, 13 H, 7-H, 8-H, Boc–C($C\underline{H_3}$)$_3$), 0.95 – 0.86 (m, 12 H, 9-H, SiC($C\underline{H_3}$)$_3$), 0.13, 0.10 (2s, 2x 3 H, Si($C\underline{H_3}$)$_2$) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$): δ = 155.8 (s, Boc–CO), 87.9 (s, C-5), 79.7 (s, C-4), 78.5 (s, Boc–$\underline{C}(CH_3)_3$), 66.3 (d, C-3), 62.9 (t, C-1), 55.5 (d, C-2), 30.6 (t, C-7), 28.5 (q, Boc–C($\underline{C}H_3$)$_3$), 25.9 (q, SiC($\underline{C}H_3$)$_3$), 22.0 (t, C-8), 18.4 (t, C-6), 18.2 (s, Si$\underline{C}$(CH$_3$)$_3$), 13.7 (q, C-9), −4.7, −5.2 (2q, Si($\underline{C}H_3$)$_2$) ppm.

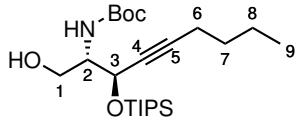
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{20}H_{40}O_4NSi$ 386.2721, found 386.2710.

IR (ATR): ν_{max} = 3442, 2957, 2931, 2853, 1695, 1503, 1463, 1391, 1366, 1250, 1166 cm^{-1}.

$[\alpha]_D^{25}$**:** -24.6° (c = 1.1; $CHCl_3$).

tert-Butyl ((*2S*,*3R*)-1-hydroxy-3-((triisopropylsilyl)oxy)non-4-yn-2-yl)-carbamate (152)

exp: 124
DL656



According to GP 20, the reaction of oxazolidine **150** (200 mg, 427 µmol) with PPTS (16.1 mg, 64.1 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 80/20), **152** as a yellowish oil (78.6 mg, 43 %, 60 % brsm).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.36 (d, J = 7.9 Hz, 1 H, N-H), 4.84 – 4.75 (m, 1 H, 3-H) 4.31 – 4.17 (m, 1 H, 2-H) 3.72 – 3.54 (m, 2 H, 1-H), 2.18 (td, J = 6.8, 2.0 Hz, 2 H, 6-H), 1.52 – 1.34 (m, 14 H, 7-H, 8-H, Boc–C($C\underline{H_3}$)$_3$), 1.19 – 0.99 (m, 28 H, 7-H, 8-H, SiCH($C\underline{H_3}$)$_2$, Si$\underline{C}$H(CH$_3$)$_2$), 0.88 (t, J = 7.1 Hz, 3 H, 9-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 155.8 (s, Boc–CO), 88.0 (s, C-5), 79.6 (s, Boc–$\underline{C}(CH_3)_3$), 78.6 (s, C-4), 66.4 (d, C-3), 63.0 (t, C-1), 56.0 (d, C-2), 30.5 (t, C-7), 28.5 (q, Boc–C($\underline{C}H_3$)$_3$), 22.0 (t, C-8), 18.4 (t, C-6), 18.08, 18.05 (2q, SiCH($\underline{C}H_3$)$_2$), 13.6 (q, C-9), 12.3 (d, Si$\underline{C}$H(CH$_3$)$_2$) ppm.

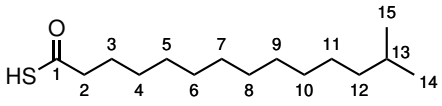
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{23}H_{46}O_4NSi$ 428.3191, found 428.3182.

IR (ATR): ν_{max} = 3441, 2958, 2934, 2865, 1697, 1503, 1365, 1247, 1167, 1087 cm^{-1}.

$[\alpha]_D^{25}$**:** -26.5° (c = 1.2; $CHCl_3$).

13-Methyltetradecanethioic *S*-acid (SI-21)

exp: 125
DL610



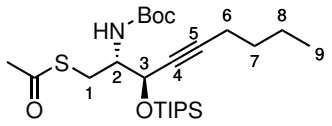
According to GP 10, the reaction of carboxylic acid **34** (200 mg, 825 µmol) with Lawesson's reagent (184 mg, 454 µmol) yielded **SI-21** as a yellowish oil (297 mg, quant.).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.59 (t, J = 7.5 Hz, 2 H, 2-H), 1.64 (p, J = 7.5 Hz, 2 H, 3-H), 1.58 – 1.43 (m, 1 H, 13-H), 1.38 – 1.20 (m, 18 H, 4-H11), 1.20 – 1.10 (m, 2 H, 12-H), 0.86 (d, J = 6.6 Hz, 6 H, 14-H, 15-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 198.4 (s, C-1), 45.9 (t, C-2), 39.2 (t, C-12), 30.1, 29.8, 29.74, 29.68, 29.5, 29.3, 28.9 (7t, C-3 to C-11), 28.1 (d, C-13), 27.5, 25.5 (2t, C-3 to C-11), 22.8 (q, C-14, C-15) ppm.

S-((*2R,3R*)-2-((*tert*-Butoxycarbonyl)amino)-3-((triisopropylsilyl)oxy)non-4-yn-1-yl) ethanethioate (153)

exp: 126
DL657



According to GP 25, the reaction of alcohol **152** (20.0 mg, 46.8 µmol) with PPh_3 (14.7 mg, 56.1 µmol), DIAD (11.9 µL, 60.8 µmol) and thioacetic acid (6.65 µL, 93.5 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 90/10), **153** as a colorless oil (13.2 mg, 58 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.86 (d, J = 9.4 Hz, 1 H, N-H), 4.71 – 4.62 (m, 1 H, 3-H), 3.93 – 3.73 (m, 1 H, 2-H), 3.38 – 3.04 (m, 2 H, 1-H), 2.34 (s, 3 H, SCOC$\underline{H}_3$), 2.20 (td, J = 6.9, 1.9 Hz, 2 H, 6-H), 1.60 – 1.35 (m, 17 H, 7-H, 8-H, Boc–C(C$\underline{H}_3$)$_3$), 1.17 – 1.03 (m, 28 H, 7-H, 8-H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.90 (t, J = 7.0 Hz, 3 H, 9-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.2 (s, S$\underline{C}$OCH$_3$), 155.7 (s, Boc–CO), 87.4 (s, C-5), 79.4 (s, Boc–$\underline{C}$(CH$_3$)$_3$), 78.5 (s, C-4), 65.3 (d, C-3), 56.5 (d, C-2), 30.64 (t, C-7), 30.60 (q, SCO$\underline{C}$H$_3$), 28.5 (q, Boc–C($\underline{C}$H$_3$)$_3$), 22.1 (t, C-8), 18.5 (t, C-6), 18.18, 18.16 (2q, SiCH($\underline{C}$H$_3$)$_2$), 13.7, (q, C-9) 12.4 (d, Si$\underline{C}$H(CH$_3$)$_2$) ppm.

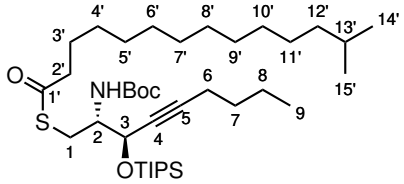
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{25}H_{48}O_4NSSi$ 486.3068, found 486.3057.

IR (ATR): ν_{max} = 2958, 2930, 2865, 1716, 1695, 1496, 1463, 1365, 1352, 1244, 1168, 1098 cm^{-1}.

$[\alpha]_D^{25}$**:** -29.4° (c = 1.1; $CHCl_3$).

S-((*2R,3R*)-2-((*tert*-Butoxycarbonyl)amino)-3-((triisopropylsilyl)oxy)non-4-yn-1-yl) 13-methyltetradecanethioate (154)

exp: 127
DL659



According to GP 25, the reaction of alcohol **152** (20.0 mg, 46.8 µmol) with PPh_3 (14.7 mg, 56.1 µmol), DIAD (11.9 µL, 60.8 µmol) and thiocarboxylic acid **SI-21** (14.7 mg, 56.1 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 97/3), **154** as a colorless oil (16.7 mg, 53 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.88 (d, J = 9.4 Hz, 1 H, N-H), 4.70 – 4.59 (m, 1 H, 3-H), 3.86 – 3.74 (m, 1 H, 2-H) 3.22 (d, J = 7.1 Hz, 2 H, 1-H), 2.66 – 2.48 (m, 2 H, 2'-H), 2.19 (td, J = 6.8, 2.0 Hz, 2 H, 6-H), 1.64 (tt, J = 9.6, 4.7 Hz, 2 H, 3'-H), 1.58 – 1.37 (m, 14 H, 7-H, 8-H, 13'-H, Boc–C(C$\underline{H}_3$)$_3$), 1.36 – 1.20 (m, 32 H, 4'-H to 11'-H), 1.20 – 1.03 (m, 24 H, 12'-H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.98 – 0.81 (m, 14 H, 9-H, 14'-H, 15'-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ =200.2 (s, C-1'), 155.6 (s, Boc–CO), 87.3 (s, C-5), 79.3 (s Boc–$\underline{C}$(CH$_3$)$_3$), 78.6 (s, C-4), 65.3 (d, C-3), 56.7 (d, C-2), 44.3 (C-2'), 39.2 (C-12'), 30.6 (t, C-7), 30.1, 29.84, 29.79, 29.77,

29.7, 29.6, 29.5, 29.41, 29.36, 29.1, 28.9 (11t, C-4' to C-11'), 28.5 (q, Boc−C($\underline{C}H_3)_3$), 28.1 (d, C-13'), 27.6, 25.5 (2t, C-4' to C-11'), 22.8 (q, C-14', C-15'), 22.1 (t, C-8), 18.5 (t, C-6), 18.19, 18.16 (2q, SiCH($\underline{C}H_3)_2$), 13.7 (q, C-9), 12.4 (d, Si$\underline{C}$H$(CH_3)_2$) ppm.

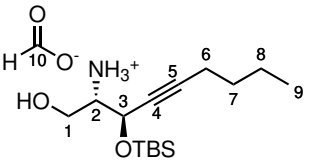
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{38}H_{74}O_4NSSi$ 668.5102, found 668.5092.

IR (ATR): ν_{max} = 2923, 2854, 1714, 1498, 1464, 1365, 1244, 1169, 1099 cm^{-1}.

$[\alpha]_D^{25}$**:** -9.26° ($c = 1.5$; $CHCl_3$).

(*2S,3R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxynon-4-yn-2-aminium formate (157)

exp: 128
DL640



According to GP 19, the reaction of oxazolidine **148** (1.16 g, 3.72 mmol) with 2,6-lutidine (1.51 mL, 13.0 mmol), 4-DMAP (45.5 mg, 372 µmol), TBSOTf (900 µL, 3.91 mmol) and TMSOTf (1.35 mL, 7.45 mmol) yielded, after flash chromatography (H_2O/MeOH+0.1 % formic acid, 40/60 → 0/100, eluting at 30/70), **157** as a yellow wax (444 mg, 42 %).

^{1}H-NMR (600 MHz**, $CDCl_3$):** δ = 8.38 (s, 1 H, 10-H), 5.27 (br. s, 7 H, N-H, O-H), 4.55 (dt, J = 4.5, 1.9 Hz, 1 H, 3-H), 3.86 (dd, J = 12.0, 3.8 Hz, 1 H, 1-H), 3.79 (dd, J = 12.0, 7.6 Hz, 1 H, 1-H), 3.47 – 3.06 (m, 1 H, 2-H), 2.21 (td, J = 7.1, 2.0 Hz, 2 H, 6-H), 1.51 – 1.45 (m, 2 H, 7-H, 8-H), 1.40 (dq, J = 9.6, 7.2 Hz, 2 H, 7-H, 8-H), 0.93 – 0.85 (m, 12 H, 9-H, SiC($\underline{C}H_3)_3$) 0.16, 0.13 (2s, 2x 3 H, Si($\underline{C}H_3)_2$)ppm.

^{13}C-NMR (151 MHz**, $CDCl_3$):** δ = 168.6 (d, C-10), 89.1 (s, C-5), 63.0 (t, C-1), 60.3 (d, C-3), 57.9 (d, C-2), 30.5 (t, C-7), 25.9 (q, SiC($\underline{C}H_3)_3$), 22.1 (t, C-8), 18.5 (t, C-6), 18.2 (s, SiC($\underline{C}H_3)_3$), 13.7 (q, C-9), −4.4, −5.0 (2q, Si($\underline{C}H_3)_2$) ppm.

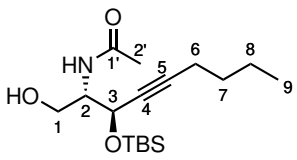
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{15}H_{32}O_2NSi$ 286.2197, found 286.2191.

IR (ATR): ν_{max} = 3154, 2955, 2929, 2857, 1576, 1463, 1345, 1251, 1065 cm^{-1}.

$[\alpha]_D^{25}$**:** -37.5° ($c = 1.1$; $CHCl_3$).

N-((*2S,3R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxynon-4-yn-2-yl)acetamide (158)

exp: 129
DL651



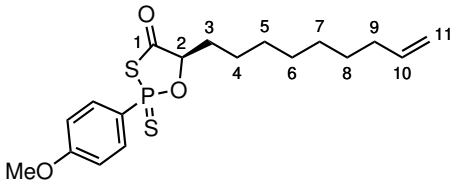
According to GP 25, the reaction of amine **157** (20 mg, 60.3 µmol) with PPh_3 (19.0 mg, 72.4 µmol), DIAD (15.9 mg, 78.4 µmol), thioacetic acid (6.44 µL, 90.5 µmol) and potassium thioacetate (13.8 mg, 121 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 0/100, eluting at 0/100), **158** as a colorless oil (15.0 mg, 41 %; contains one equivalent of PPh_3O).

^{1}H-NMR (300 MHz, **$CDCl_3$**): δ = 6.32 (d, J = 7.8 Hz, 1 H, N-H), 4.75 – 4.64 (m, 1 H, 3-H), 4.28 (dd, J = 11.6, 2.9 Hz, 1 H, 1-H), 3.97 – 3.86 (m, 1 H, 2-H), 3.64 (ddd, J = 11.5, 3.9, 1.0 Hz, 1 H, 1-H), 2.20 (td, J = 6.9, 2.0 Hz, 2 H, 6-H), 2.01 (s, 3 H, 2'-H), 1.60 – 1.31 (m, 6 H, 7-H, 8-H), 0.96 – 0.85 (m, 13 H, 9-H, $SiC(C\underline{H}_3)_3$), 0.14, 0.10 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (75 MHz, **$CDCl_3$**): δ = 170.2 (s, C-1'), 88.2 (s, C-5), 78.2 (s, C-4), 66.0 (d, C-3), 62.8 (t, C-1), 54.6 (d, C-2), 30.6 (t, C-7), 25.8 (q, $SiC(\underline{C}H_3)_3$), 23.5 (q, C-2'), 22.0 (t, C-8), 18.4 (t, C-6), 18.2 (s, $Si\underline{C}(CH_3)_3$), 13.6 (q, C-9), −4.6, −5.2 (2q, $Si(\underline{C}H_3)_2$) ppm.

(*S*)-2-(4-Methoxyphenyl)-5-(non-8-en-1-yl)-1,3,2-oxathiaphospholan-4-one-2-sulfide (159)

exp: 130
DL678



According to GP 10, the reaction of carboxylic acid **56** (42.0 mg, 208 µmol) with Lawesson's reagent (46.3 mg, 114 µmol) yielded **159** as a yellowish oil (90 mg, quant.).

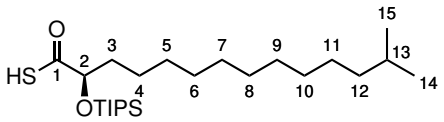
^{1}H-NMR (300 MHz, **$CDCl_3$**): δ = 8.17 – 7.59 (m, 2 H, Ar-H), 6.98 – 6.68 (m, 2 H, Ar-H), 5.92 – 5.69 (m, 1 H, 10-H), 5.09 – 4.82 (m, 2 H, 2-H, 11-H), 3.90, 3.88 (2 s, 3 H, $OC\underline{H}_3$), 2.11 – 1.98 (m, 2 H, 3-H, 9-H) 1.70 – 1.46 (m, 2 H, 3-H, 9-H), 1.43 – 1.05 (m, 10 H, 4-H to 8-H) ppm.

^{13}C-NMR (75 MHz, **$CDCl_3$**): δ = 199.6 (d, J = 9.2 Hz, C-1), 199.2 (d, J = 7.6 Hz, C-1), 139.2 (d, C-10), 139.1 (d, C-10), 134.8 (dd, J = 15.6 Hz, C-Ar), 133.9 (dd, J = 15.5 Hz, C-Ar), 129.2 (s, C-Ar) 128.3 (s, C-Ar), 114.5 – 114.3 (m, C-Ar, C-11), 114.2 (dd, J = 3.0 Hz, C-Ar), 89.33 (dd, J = 9.9 Hz, C-2), 85.7 (dd, J = 8.6 Hz, C-2), 55.78, 55.75 (2s, $O\underline{C}H_3$), 33.9 (t, C-9), 29.2, 29.09, 29.05, 29.02, 28.98, 28.95 (6t, C-4 to C-8), 25.11 (dt, J = 2.5 Hz, C-3) ppm.

^{31}P-NMR (203 MHz, **$CDCl_3$**): δ = 98.2 – 97.7 (m), 95.8 (t, J = 15.3 Hz) ppm.
The ^{31}P-atom contains a stereocenter, resulting in two diastereomers.

(*R*)-13-Methyl-2-((triisopropylsilyl)oxy)tetradecanethioic *S*-acid (160)

exp: 131
DL700



According to GP 10, the reaction of carboxylic acid **61** (32 mg, 77.2 µmol) with Lawesson's reagent (17.2 mg, 42.4 µmol) yielded **160** as a colorless oil (48.2 mg, quant.).The product contains 0.5 equivalents of Lawesson's reagent.

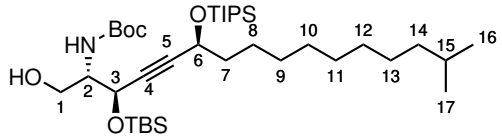
^{1}H-NMR (300 MHz, **$CDCl_3$**): δ = 4.25 (dd, J = 6.5, 4.5, 6.5 Hz, 1 H, 2-H), 1.86 – 1.62 (m, 3 H, 3-H), 1.62 – 1.40 (m, 5 H, 4-H to 11-H, 13-H), 1.40 – 1.20 (m, 21 H, 4-H to 11-H), 1.20 – 0.98 (m, 27 H, 4-H to 12-H, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$), 0.87 (d, J = 6.6 Hz, 8 H, 14-H, 15-H) ppm.

^{13}C-NMR (75 MHz, **$CDCl_3$**): δ = 205.2 (s, C-1), 79.1 (d, C-2), 39.2 (t, C-12), 36.2 (t, C-3), 30.1, 29.82, 29.78, 29.75, 29.72, 29.66, 29.5 (8t, C-4 to C-11), 28.1 (d, C-13), 27.6, 23.6 (2t, C-4 to C-11), 22.8

(q, C-14, C-15), 18.14, 18.10 (2q, SiCH($\underline{C}H_3)_2$), 12.5 (d, Si$\underline{C}H(CH_3)_2$) ppm.

tert-Butyl ((*2S,3R,6S*)-3-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yn-2-yl)carbamate (161)

exp: 132
DL666



According to GP 20, the reaction of alkyne **109** (1.50 g, 2.11 mmol) with PPTS (53.1 mg, 211 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 85/15), **161** as a colorless oil (310 mg, 22 %, 66 % brsm).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.38 (d, J = 7.7 Hz, 1 H, N-H), 4.80 – 4.63 (m, 1 H, O-H), 4.50 (td, J = 6.2, 1.6 Hz, 2 H, 3-H, 6-H), 4.37 – 4.20 (m, 1 H, 2-H), 4.20 – 3.87 (m, 1 H, 1-H), 3.73 – 3.55 (m, 1 H, 1-H), 1.75 – 1.57 (m, 2 H, 7-H), 1.54 – 1.39 (m, 12 H, 15-H, Boc–C($\underline{C}H_3)_3$), 1.37 – 1.19 (m, 18 H, 8-H to 13-H), 1.18 – 1.00 (m, 46 H, 14-H, SiCH($\underline{C}H_3)_2$, Si$\underline{C}H(CH_3)_2$), 0.90 (s, 9 H, SiC($\underline{C}H_3)_3$), 0.86 (d, J = 6.7 Hz, 6 H, 16-H, 17-H), 0.14, 0.11 (2s, 2x 3 H, Si($\underline{C}H_3)_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 154.0 (s, Boc–CO), 95.1 (s, C-5), 89.0 (s, C-4), 81.8 (s, Boc–$\underline{C}(CH_3)_3$) 65.0, 64.8 (2d, C-3, C-6), 63.2 (t, C-1), 60.5 (d, C-2), 39.2 (t, C-14), 37.1 (t, C-7), 30.1, 29.8, 29.7, 29.6, 29.5 (5t, C-8 to C-13) 28.54, 28.49 (2q, Boc–C($\underline{C}H_3)_3$), 28.1 (d, C-15), 27.5 (t, C-8 to C-13), 25.8 (q, SiC($\underline{C}H_3)_3$), 22.8 (q, C-16, C-17), 18.2 (q, SiCH($\underline{C}H_3)_2$), 12.4 (d, Si$\underline{C}H(CH_3)_2$), −4.8, −5.3 (2q, Si($\underline{C}H_3)_2$) ppm.

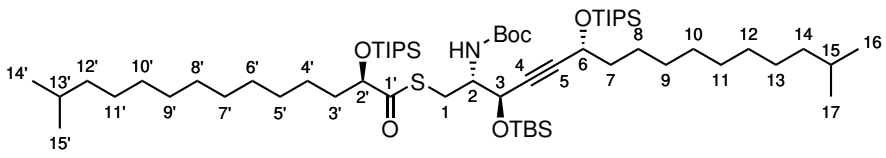
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{37}H_{76}O_5NSi_2$ 670.5257, found 670.5246.

IR (ATR): ν_{max} = 2927, 2864, 1696, 1462, 1390, 1366, 1251, 1170 cm^{-1}.

$[\alpha]_D^{25}$**:** -35.6° (c = 1.0; $CHCl_3$).

S-((*2R,3R,6S*)-2-((*tert*-Butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yn-1-yl) (*R*)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanethioate (162)

exp: 133
DL718



DIAD (7.03 µL, 35.8 µmol) was added to a solution of PPh_3 (10.2 mg, 38.8 µmol) in THF (194 µL) at 0 °C and the solution stirred at 0 °C for 30 min, during which a precipitate formed. To this suspension a mixture of alcohol **161** (20.0 mg, 29.8 µmol) and thiocarboxylic acid **160** (23.1 mg, 53.7 µmol) in CH_2Cl_2 (134 µL) was added and the clear solution stirred at r.t. for 24 h and at 100 °C for 60 min. CH_2Cl_2 and sat. $NaHCO_3$ solution were added, the aqueous phase extracted with CH_2Cl_2, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 98/2 → 50/50, eluting at 98/2) to yield **162** as a colorless solid (8.72 mg, 27 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.88 (d, J = 8.4 Hz, 1 H, N-H), 4.66 – 4.62 (m, 1 H, 3-H), 4.55 – 4.47 (m, 2 H, 6-H), 4.42 – 4.38 (m, 1 H, 2'-H), 3.78 – 3.71 (m, 1 H, 2-H), 3.28 – 3.20, 3.16 – 3.10 (2m, 2x 1 H, 1-H), 1.88 – 1.74 (m, 2 H, 3'-H), 1.73 – 1.63 (m, 4 H, 7-H, 3'-H), 1.59 – 1.38 (m, 42 H, 8-H to 13-H, 15-H, 4'-H to 11'-H, 13'-H, Boc–C($C\underline{H}_3$)$_3$), 1.34 – 1.20 (m, 86 H, 8-H to 13-H, 4'-H to 11'-H), 1.19 – 1.02 (m, 102 H, 14-H, 12'-H, SiCH($C\underline{H}_3$)$_2$, Si$C\underline{H}$(CH_3)$_2$), 0.92 (s, 12 H, SiC($C\underline{H}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 27 H, 16-H, 17-H, 14'-H, 15'-H), 0.11, 0.09 (2s, 2x 3 H, Si($C\underline{H}_3$)$_2$) ppm.

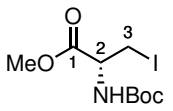
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 206.3 (s, C-1'), 88.2 (s, C-5), 82.2 (s, C-4), 78.9 (d, C-2'), 64.5 (d, C-3), 63.3 (d, C-6), 56.7 (d, C-2), 39.2 (t, C-14, C-12'), 39.1 (t, C-7), 36.5 (t, C-3'), 30.5, 30.11, 30.08, 29.9, 29.81, 29.78, 29.7, 29.61, 29.57 (9t, C-8 to C-13, C-4' to C-11'), 28.6 (q, Boc–C($\underline{C}H_3$)$_3$), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 27.1 (t, C-1), 25.9 (q, SiC($\underline{C}H_3$)$_3$), 22.8 (q, C-16, C-17, C-14', C-15'), 18.21, 18.17 (s+2q, Si$\underline{C}$(CH_3)$_3$, SiCH($\underline{C}H_3$)$_2$), 12.5, 12.4 (2d, Si$\underline{C}$H(CH_3)$_2$), −4.8 (q, Si($\underline{C}H_3$)$_2$) ppm.

4.7 Synthesis of sulfonic acids — "late stage strategy"

4.7.1 Synthesis of cysteic acid derivatives

Methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (165)

exp: 134
DL181



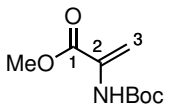
Imidazole (40.4 mg, 593 µmol) was added to a solution of PPh_3 (156 mg, 593 µmol) in CH_2Cl_2 (1.98 µL) and the mixture was stirred at r.t. until all imidazole was dissolved. The solution was cooled to 0 °C, I_2 (150 mg, 593 µmol) was added and the now brown reaction stirred at r.t. for 15 min. A solution of alcohol **83** (100 mg, 456 µmol) in CH_2Cl_2 (456 µL) was added and the reaction stirred in the dark at r.t. for 3 h. The mixture was filtered over a pad of silica, the volatiles removed *in vacuo* and the residue purified by flash chromatography (cyclohexane/EtOAc 50/1 → 10/1) to yield **165** as a yellowish oil (88.4 mg, 59 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.35 (d, J = 7.8 Hz, 1 H, N-H), 4.51 (p, J = 4.0 Hz, 1 H, 2-H), 3.81 (s, 3 H, OC$\underline{H}_3$), 3.64 – 3.48 (m, 2 H, 1-H), 1.46 (s, 9 H, Boc–C($C\underline{H}_3$)$_3$) ppm.

The analytical data is consistent with literature reports.[150]

Methyl 2-((*tert*-butoxycarbonyl)amino)acrylate (168)

exp: 135
DL181



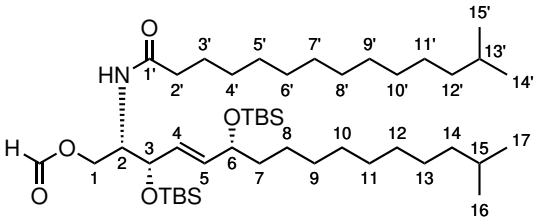
168, a side product in the synthesis of **165**, was isolated as a colorless oil (4.2 mg, 5 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.16 (s, 1 H, 3-H), 5.73 (d, J = 1.6 Hz, 1 H, N-H), 3.83 (s, 3 H, OC$\underline{H}_3$), 1.49 (s, 9 H, Boc–C($C\underline{H}_3$)$_3$) ppm.

4.7.2 Synthesis of (*3S*)-OH sulfonolipids

(*2S,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-15-methyl-2-(13-methyltetradecanamido)hexadec-4-en-1-yl formate (170)

exp: 136
DL377



2,6-Lutidine (9.21 µL, 79.5 µmol) and Tf_2O (8.06 µL, 47.7 µL) were added to a solution of amide **125** (30.0 mg, 39.8 µmol) in DMF (200 µL) at −10 °C and the mixture stirred for 30 min. 15-Crown-5 (78.9 µL, 398 µmol) and sodium ethanesulfonate[180] (26.3 mg, 198 µmol) were added and the orange suspension was stirred at r.t. for 5 d. Citric acid solution (10 wt − % in H_2O) was added, the aqueous phase extracted with EtOAc, the combined organic phase washed with H_2O, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 10/1) to yield **170** as a colorless oil (8.3 mg, 27 %).

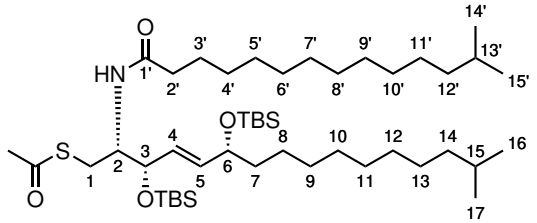
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1 H, HCO), 5.70 – 5.60 (m, 1 H, 5-H), 5.52 (dd, J = 15.5, 6.0 Hz, 1 H, 4-H), 4.37 (dt, J = 5.9, 1.8 Hz, 1 H, 3-H), 4.26 – 4.15 (m, 2 H, 1-H, 2-H), 4.13 – 4.05 (m, 2 H, 1-H, 6-H), 2.15 (t, J = 7.7 Hz, 2 H, 2'-H), 1.67 – 1.54 (m, 4 H, 7-H, 3'-H), 1.54 – 1.46 (m, 2 H, 15-H, 13'-H), 1.46 – 1.35 (m, 2 H, 8-H to 13-H, 4'-H to 11'-H), 1.34 – 1.20 (m, 30 H, 8-H to 13-H, 4'-H to 11'-H), 1.14 (q, J = 6.8 Hz, 4 H, 14-H, 12'-H), 0.91, 0.88 (2s, 2x 9 H, $SiC(CH_3)_3$), 0.86 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.06, 0.04, 0.03, 0.01 (4s, 3 H, $Si(CH_3)_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 172.9 (s, C-1'), 160.8 (d, HCO), 136.3 (d, C-5'), 128.1 (d, C-4), 72.6 (d, C-6), 70.7 (d, C-3), 62.4 (t, C-1), 52.3 (d, C-2), 39.2 (t, C-14, C-12'), 38.4 (t, C-7), 36.9 (t, C-2'), 30.10, 30.07, 29.9, 29.83, 29.79, 29.7, 29.53, 29.45 (8t, C-8 to C-13, C-3' to C-11'), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.0 (q, $SiC(CH_3)_3$), 25.8, 25.3 (2t, C-8 to C-13, C-4' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.3, 18.2 (2s, $SiC(CH_3)_3$) −4.1, −4.3, −4.9, −5.1 (4q, $Si(CH_3)_2$) ppm.

HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{45}H_{91}NO_5NaSi_2$ 804.6328, found 804.6333.

S-((*2R,3S,6R,E*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-15-methyl-2-(13-methyltetradecanamido)hexadec-4-en-1-yl) ethanethioate (171)

exp: 137
DL347



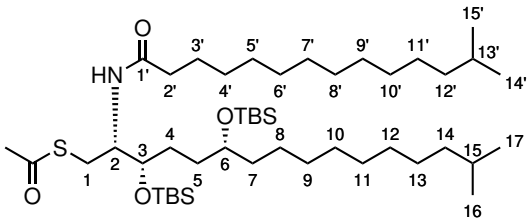
According to GP 25, the reaction of amide **125** (40.0 mg, 53.0 µmol) with PPh_3 (16.7 mg, 58.3 µmol), DIAD (13.7 µL, 68.9 µmol), thioacetic acid (4.15 µL, 58.3 µmol) and potassium thioacetate (18.2 mg, 159 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 20/1 → 10/1), **171** as a colorless oil (22.9 mg, 53 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.71 (d, J = 8.5 Hz, 1 H, N-H), 5.69 – 5.60 (m, 1 H, 5-H), 5.59 – 5.47 (m, 1 H, 4-H), 4.33 (dd, J = 5.4, 3.1 Hz, 1 H, 3-H), 4.10 (q, J = 6.4, 5.9 Hz, 1 H, 6-H), 4.06 – 3.96 (m, 1 H, 2-H), 3.12 – 2.94 (m, 2 H, 1-H), 2.33 (s, 3 H, SCOC$\underline{H}_3$), 2.16 – 2.01 (m, 2 H, 2'-H), 1.71 – 1.62 (m, 1 H, 7-H), 1.60 – 1.44 (m, 3 H, 7-H, 15-H, 13'-H), 1.46 – 1.38 (m, 2 H, 8-H to 13-H, 4'-H to 11'-H), 1.34 – 1.19 (m, 34 H, 8-H to 13-H, 4'-H to 11'-H), 1.20 – 1.08 (m, 4 H, 14-H, 12'-H), 0.92, 0.89 (2s, 2x 9 H, SiC($\underline{CH}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.10, 0.05, 0.04, 0.03 (4s, 2x 3 H, Si($\underline{CH}_3$)$_2$) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 196.8 (s, S$\underline{C}$OCH$_3$), 172.9 (s, C-1'), 136.4 (d, C-5), 127.6 (d, C-4), 72.8, 72.7 (2d, C-3, C-6), 54.6 (d, C-2), 39.2, (t, C-14, C-12'), 38.5 (t, C-7), 37.0 (t, C-2'), 30.7 (q, SCO$\underline{C}$H$_3$), 30.10, 30.07, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5 (7t, C-1, C-8 to C-13, C-3' to C-11'), 28.1 (d, C-15, C-13'), 27.6, 27.1 (2t, C-8 to C-13, C-3' to C-11'), 26.0, 25.8 (2q, SiC($\underline{C}$H$_3$)$_3$), 25.3 (t, C-8 to C-13, C-3' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.4, 18.2 (2s, Si$\underline{C}$(CH$_3$)$_3$), −4.21, −4.23, −4.6, −4.8 (4q, Si($\underline{C}$H$_3$)$_2$) ppm.

S-(*2R,3S,6R*)-3,6-Bis((*tert*-butyldimethylsilyl)oxy)-15-methyl-2-(13-methyltetradecanamido)hexadecyl) ethanethioate (172)

exp: 138
DL419



According to GP 25, the reaction of amide **135** (93.7 mg, 124 µmol) with PPh_3 (39.0 mg, 149 µmol), DIAD (31.9 µL, 161 µmol), thioacetic acid (9.70 µL, 136 mmol) and KSAc (42.5 mg, 371 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 100/0 → 80/20, eluting at 90/10), **172** as a colorless oil (9.70 mg, 10 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.76 (d, J = 9.0 Hz, 1 H, N-H), 4.14 – 4.01 (m, 1 H, 3-H), 3.83 – 3.73 (m, 1 H, 6-H), 3.67 – 3.51 (m, 1 H, 2-H), 3.18 – 3.13 (m, 1 H, 1-H), 2.95 (dd, J = 14.4, 3.5 Hz, 1 H, 1-H), 2.33 (s, 3 H, SCOC$\underline{H}_3$), 2.09 (q, J = 8.0 Hz, 2 H, 2'-H), 1.80 – 1.46 (m, 5 H, 4-H to 5-H, 7-H to 13-H, 15-H, 3'-H to 11'-H, 13'-H), 1.46 – 1.18 (m, 37 H, 7-H to 13-H, 15-H, 3'-H to 11'-H, 13'-H), 1.14 (q, J = 6.8 Hz, 4 H, 14-H, 12'-H), 0.93, 0.87 (2s, 2x 9 H, SiC($\underline{CH}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 23 H, 16-H, 17-H, 14'-H, 15'-H), 0.11, 0.09, 0.06, 0.02 (4s, 4x 3 H, Si($\underline{CH}_3$)$_2$) ppm.

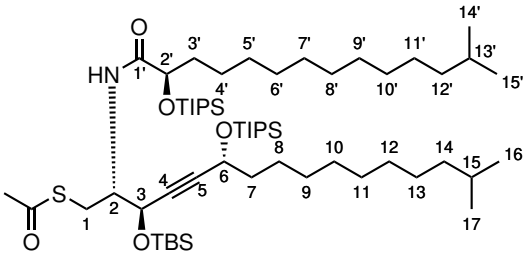
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 197.4 (s, S$\underline{C}$OCH$_3$), 172.7 (s, C-1'), 74.9 (d, C-3), 72.2 (d, C-6), 52.8 (d, C-2), 39.2 (t, C-14, C-12'), 37.2 (t, C-4, C-5, C-7), 37.1 (t, C-3'), 32.4, 31.3 (2t, C-4, C-5, C-7), 30.7 (q, SCO$\underline{C}$H$_3$), 30.2, 30.1, 29.98, 29.85, 29.83, 29.80, 29.66, 29.55 (8t, C-8 to C-13, C-4' to C-11'), 29.5 (t, C-1), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.1 (q, SiC($\underline{C}$H$_3$)$_3$), 22.8 (q, C-16, C-17, C-14', C-15'), 18.2 (s, Si$\underline{C}$(CH$_3$)$_3$) ppm.

IR (ATR) ν_{max}: 2924, 2853, 1697, 1644, 1522, 1463, 1254, 1080 cm^{-1}.

4.7.3 Synthesis of (*3R*)-OH sulfonolipids

S-((*2R,3R,6R*)-3-((*tert*-Butyldimethylsilyl)oxy)-15-methyl-2-((*R*)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamido)-6-((triisopropylsilyl)oxy)hexadec-4-yn-1-yl) ethanethioate (174)

exp: 139
DL747



According to GP 25, the reaction of amide **139** (400 mg, 414 µmol) with PPh_3 (217 mg, 827 µmol), DIAD (118 µL, 786 µmol) and thioacetic acid (118 µL, 1.65 mmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 90/10, eluting at 90/10), **174** as a colorless oil (310 mg, 73 %).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.95 (d, J = 9.9 Hz, 1 H, N-H), 4.54 – 4.48 (m, 2 H, 3-H, 6-H), 4.34 (dd, J = 5.6, 3.5 Hz, 1 H, 2'-H), 4.32 – 4.28 (m, 1 H, 2-H), 3.42 (dt, J = 13.8, 3.3 Hz, 1 H, 1-H), 3.09 (dd, J = 13.8, 9.5 Hz, 1 H, 1-H), 2.29 (s, 3 H, SCOC$\underline{H}_3$), 1.90 – 1.82 (m, 1 H, 3'-H), 1.74 – 1.56 (m, 3 H, 3'-H, 7-H), 1.56 – 1.47 (m, 3 H, 8-H to 13-H, 15-H, 4'-H to 11'-H, 13'-H), 1.35 – 1.19 (m, 10 H, 8-H to 13-H, 4'-H to 11'-H), 1.17 – 1.04 (m, 37 H, 14-H, 12'-H, SiCH(C$\underline{H}_3$)$_2$, SiC$\underline{H}$(CH$_3$)$_2$), 0.91 (s, 9 H, SiC(C$\underline{H}_3$)$_3$), 0.86 (d, J = 6.6 Hz, 13 H, 16-H, 17-H, 14'-H, 15'-H), 0.16, 0.10 (2s, 2x 3 H, Si(C$\underline{H}_3$)$_2$) ppm.

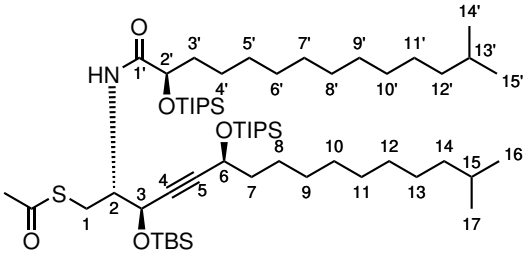
^{13}C-NMR (151 MHz, $CDCl_3$): δ = 195.0 (s, S$\underline{C}$OCH$_3$), 173.6 (s, C-1'), 89.1 (s, C-5), 81.6 (s, C-4), 73.7 (d, C-2'), 65.6 (d, C-6), 63.2 (d, C-3), 52.7 (d, C-2), 39.2 (t, C-14, C-12'), 35.8 (t, C-3'), 30.6 (q, SCO$\underline{C}$H$_3$), 30.1, 29.87, 29.85, 29.81, 29.79, 29.66, 29.45 (7t, C-8 to C-13, C-4' to C-11'), 29.5 (t, C-1), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.0 (q, SiC($\underline{C}$H$_3$)$_3$), 22.8 (q, C-16, C-17, C-14', C-15'), 18.3, 18.20, 18.16 (2q, s, SiCH($\underline{C}$H$_3$)$_2$, Si$\underline{C}$(CH$_3$)$_3$), 12.43, 12.40 (2d, Si$\underline{C}$H(CH$_3$)$_2$), −4.3 (q, Si($\underline{C}$H$_3$)$_2$) ppm.

IR (ATR) ν_{max}: 2925, 2864, 1697, 1683, 1507, 1463, 1097 cm^{-1}.

$[\alpha]_D^{25}$**:** -3.42° (c = 1.0; $CHCl_3$).

S-((*2R,3R,6S*)-3-((*tert*-Butyldimethylsilyl)oxy)-15-methyl-2-((*R*)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamido)-6-((triisopropylsilyl)oxy)hexadec-4-yn-1-yl) ethanethioate (175)

exp: 140
DL739



According to GP 25, the reaction of amide **140** (40 mg, 41.4 µmol) with PPh_3 (21.7 mg, 82.8 µmol), DIAD (15.4 µL, 78.6 µmol) and thioacetic acid (11.8 µL, 166 µmol) yielded, after flash chromatography

(cyclohexane/EtOAc 98/2 → 90/10, eluting at 90/10), **175** as a colorless oil (25.1 mg, 59 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.94 (d, J = 9.8 Hz, 1 H, N-H), 4.54 – 4.49 (m, 2 H, 3-H, 6-H), 4.39 – 4.26 (m, 2 H, 2-H, 2'-H), 3.43 (dd, J = 13.9, 3.7 Hz, 1 H, 1-H), 3.10 (dd, J = 13.8, 9.6 Hz, 1 H, 1-H), 2.29 (s, 3 H, $SCOC\underline{H}_3$), 1.82 – 1.59 (m, 6 H, 7-H to 13-H, 3'-H to 11'-H), 1.59 – 1.37 (m, 9 H, 7-H to 13-H, 15-H, 3'-H to 11'-H, 13'-H), 1.37 – 1.18 (m, 35 H, 7-H to 13-H, 3'-H to 11'-H), 1.18 – 1.04 (m, 53 H, 14-H, 12'-H, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$), 0.91 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.86 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.16, 0.10 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

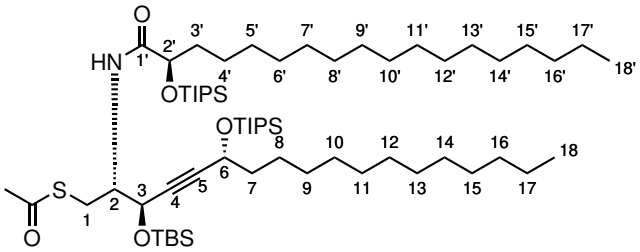
^{13}C-NMR (126 MHz, $CDCl_3$): δ = 194.9 (s, $S\underline{C}OCH_3$), 173.6 (s, C-1'), 89.0 (s, C-5), 81.6 (s, C-4), 73.7 (d, C-2'), 65.7 (d, C-6), 63.3 (d, C-3), 52.7 (d, C-2), 39.2 (t, C-14, C-12'), 35.8 (t, C-3'), 30.6 (q, $SCO\underline{C}H_3$), 30.1, 29.9, 29.85, 29.80, 29.7 (5t, C-8 to C-13, C-4' to C-11'), 29.4 (t, C-1), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.0 (q, $SiC(\underline{C}H_3)_3$), 23.6 (t, C-8 to C-13, C-4' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.3, 18.20, 18.17 (2q, s, $SiCH(\underline{C}H_3)_2$, $Si\underline{C}(CH_3)_3$), 12.5, 12.4 (2d, $Si\underline{C}H(CH_3)_2$), −4.3, −5.0 (2q, $Si(\underline{C}H_3)_2$) ppm.

IR (ATR): ν_{max} = 2924, 2864, 1733, 1697, 1503, 1463, 1252, 1093 cm^{-1}.

$[\alpha]_D^{25}$**:** -17.1° (c = 1.1; $CHCl_3$).

S-((*2R,3R,6R*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-((triisopropylsilyl)oxy)-2-((*R*)-2-((triisopropylsilyl)oxy)octadecanamido)octadec-4-yn-1-yl) ethanethioate (176)

exp: 141
DL774



According to GP 25, the reaction of amide **141** (65.0 mg, 63.5 µmol) with PPh_3 (66.6 mg, 254 µmol), DIAD (43.4 µL, 241 µmol) and thioacetic acid (36.0 µL, 508 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 90/10, eluting at 90/10), **176** as a colorless oil (47.9 mg, 53 %, contains 1.30 equiv PPh_3).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.95 (d, J = 9.9 Hz, 1 H, N-H), 4.53 – 4.47 (m, 2 H, 3-H, 6-H), 4.40 – 4.27 (m, 2 H, 2-H, 2'-H), 3.43 (dd, J = 13.9, 3.9 Hz, 1 H, 1-H), 3.10 (dd, J = 13.9, 9.6 Hz, 1 H, 1-H), 2.28 (s, 3 H, $SCOC\underline{H}_3$), 1.86 (tt, J = 12.4, 3.8 Hz, 1 H, 3'-H), 1.73 – 1.59 (m, 3 H, 7-H, 3'-H), 1.52 – 1.34 (m, 4 H, 8-H to 17-H, 4'-H to 17'-H), 1.32 – 1.18 (m, 68 H, 8-H to 17-H, 4'-H to 17'-H), 1.16 – 1.02 (m, 64 H, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$), 0.90 (s, 9 H, $SiC(C\underline{H}_3)_3$), 0.87 (t, J = 6.9 Hz, 6 H, 18-H, 18'-H), 0.15, 0.09 (2s, 2x 3 H, $Si(C\underline{H}_3)_2$) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 195.0 (s, $S\underline{C}OCH_3$), 173.6 (s, C-1'), 88.9 (s, C-5), 81.5 (s, C-4), 73.6 (d, C-2'), 65.6 (d, C-6), 63.2 (d, C-3, C-6), 52.6 (d, C-2), 39.0 (t, C-7), 35.7 (t, C-3'), 32.0 (t, C-8 to C-17, C-4' to C-17') , 30.5 (q, $SCO\underline{C}H_3$), 29.83, 29.79, 29.76, 29.73, 29.6, 29.54, 29.49 (7t, C-1, C-8 to C-17, C-4' to C-17'), 25.9 (q, $SiC(\underline{C}H_3)_3$), 25.1, 23.4, 22.8 (3t, C-8 to C-17, C-4' to C-17'), 18.22, 18.16 (2q, $SiCH(\underline{C}H_3)_2$), 17.8 (s, $Si\underline{C}(CH_3)_3$), 14.2 (q, C-17, C-18'), 12.38, 12.34 (2d, $Si\underline{C}H(CH_3)_2$), −4.3, −5.0 (2q, $Si(\underline{C}H_3)_2$) ppm.

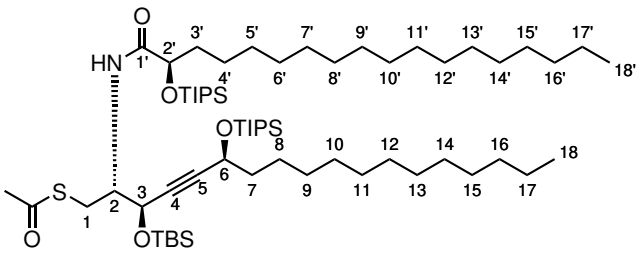
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{62}H_{125}NNaO_5SSi_3$ 1102.8478, found 1102.8518.

IR (ATR) ν_{max}: 2924, 2854, 1671, 1508, 1463, 1433, 1214, 1102 cm^{-1}.

$[\alpha]_D^{25}$**:** -6.28° ($c = 1.0$; $CHCl_3$).

S-((*2R,3R,6S*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-((triisopropylsilyl)oxy)-2-((*R*)-2-((triisopropylsilyl)oxy)octadecanamido)octadec-4-yn-1-yl) ethanethioate (177)

exp: 142
DL775



According to GP 25, the reaction of amide **142** (100 mg, 97.8 µmol) with PPh_3 (103 mg, 391 µmol), DIAD (72.9 µL, 372 µmol) and thioacetic acid (55.6 µL, 782 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 98/2 → 90/10, eluting at 90/10), **177** as a colorless oil (95.6 mg, 69 %, contains 1.26 equiv PPh_3).

^{1}H-NMR (500 MHz**, $CDCl_3$):** δ = 6.96 (d, J = 9.9 Hz, 1 H, N-H), 4.53 – 4.47 (m, 2 H, 3-H, 6-H), 4.37 – 4.26 (m, 2 H, 2-H, 2'-H), 3.41 (dd, J = 13.8, 4.0 Hz, 1 H, 1-H), 3.08 (dd, J = 13.8, 9.5 Hz, 1 H, 1-H), 2.28 (s, 3 H, $SCOCH_3$), 1.86 (ddd, J = 16.8, 8.8, 3.8 Hz, 1 H, 3'-H), 1.75 – 1.58 (m, 3 H, 7-H, 3'-H), 1.54 – 1.34 (m, 4 H, 8-H to 17-H, 4'-H to 17'-H), 1.34 – 1.21 (m, 68 H, 8-H to 17-H, 4'-H to 17'-H), 1.15 – 1.01 (m, 64 H, $SiCH(CH_3)_2$, $SiCH(CH_3)_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 0.87 (t, J = 6.9 Hz, 6 H, 18-H, 18'-H), 0.16, 0.09 (2s, 2x 3 H, $Si(CH_3)_2$) ppm.

^{13}C-NMR (126 MHz**, $CDCl_3$):** δ = 195.0 (s, $SCOCH_3$), 173.6 (s, C-1'), 89.1 (s, C-5), 81.6 (s, C-4), 73.6 (d, C-2'), 65.6 (d, C-6), 63.2 (d, C-3), 52.6 (d, C-2), 38.9 (t, C-7), 35.7 (t, C-3'), 32.1 (t, C-8 to C-17, C-4' to C-17') 30.6 (q, $SCOCH_3$), 29.84, 29.80, 29.77, 29.73, 29.63, 29.56, 29.50 (7t, C-1, C-8 to C-17, C-4' to C-17'), 25.9 (q, $SiC(CH_3)_3$), 25.1, 23.4, 22.8 (3t, C-8 to C-17, C-4' to C-17'), 18.23, 18.17 (2q, $SiCH(CH_3)_2$), 17.8 (s, $SiC(CH_3)_3$), 14.3 (q, C-17, C-18'), 12.39, 12.35 (2d, $SiCH(CH_3)_2$), −4.3, −5.0 (2q, $Si(CH_3)_2$) ppm.

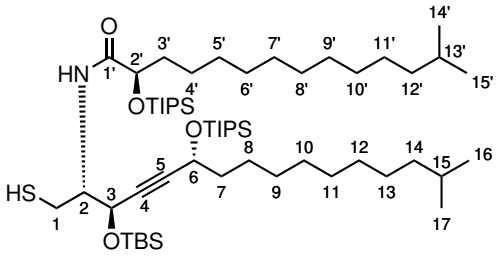
HRMS (ESI-TOF): calculated for $[M + Na]^+$ $C_{62}H_{125}NNaO_5SSi_3$ 1102.8478, found 1102.8516.

IR (ATR) ν_{max}: 2924, 2854, 1697, 1507, 1463, 1433, 1102 cm^{-1}.

$[\alpha]_D^{25}$**:** -15.8° ($c = 1.0$; $CHCl_3$).

(*R*)-*N*-((*2R,3R,6R*)-3-(*tert*-Butyldimethylsilyl)oxy)-1-mercapto-15-methyl-6-(-(triisopropylsilyl)oxy)hexadec-4-yn-2-yl)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamide (SI-22)

exp: 143
DL748



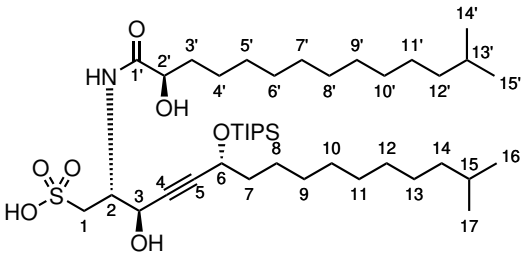
A solution of LiOH (1.87 mg, 78.1 µmol) in H_2O was added to a solution of thioacetate **174** (20.0 mg, 19.5 µmol) in THF/MeOH (1/1, 390 µL) at 0 °C and the reaction mixture stirred at 0 °C for 20 min. NH_4Cl solution was added, the aqueous phase extracted with CH_2Cl_2, the combined organic phase washed with brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc 98/2 → 90/10, eluting at 98/2) to yield **SI-22** as a colorless solid (15.4 mg, 80 %).

^{1}H-NMR (500 MHz**, CDCl$_3$):** δ = 7.04 (d, J = 9.5 Hz, 1 H, N-H), 4.66 (d, J = 4.5 Hz, 1 H, 3-H), 4.51 – 4.41 (m, 1 H, 6-H), 4.37 (dd, J = 5.7, 3.6 Hz, 1 H, 2'-H), 4.17 (dtd, J = 9.3, 6.5, 6.0, 3.3 Hz, 1 H, 2-H), 2.88 – 2.78 (m, 2 H, 1-H), 1.93 – 1.81 (m, 1 H, 3'-H), 1.72 – 1.61 (m, 2 H, 7-H, 3'-H), 1.56 – 1.39 (m, 5 H, 8-H to 13-H, 4'-H to 11'-H, 15-H, 13-H), 1.37 – 1.19 (m, 44 H, 8-H to 13-H, 4'-H to 11'-H), 1.18 – 1.02 (m, 60 H, 14-H, 12'-H, SiCH($\underline{C}H_3)_2$, Si$\underline{C}$H$(CH_3)_2$), 0.89 (s, 9 H, SiC($C\underline{H_3})_3$), 0.86 (d, J = 6.6 Hz, 15 H, 16-H, 17-H, 14'-H, 15'-H), 0.15, 0.10 (2s, 2x 3 H, Si($C\underline{H_3})_2$) ppm.

^{13}C-NMR (126 MHz**, CDCl$_3$):** δ = 173.9 (s, C-1'), 89.0 (s, C-5), 81.8 (s, C-4), 73.9 (d, C-2'), 64.9 (d, C-3), 63.2 (d, C-6), 55.9 (d, C-2), 39.2 (t, C-14, C-12'), 39.1 (t, C-7), 35.6 (t, C-3'), 30.1, 29.89, 29.86, 29.83, 29.80, 29.77, 29.68, 29.65 (8t, C-8 to C-13, C-4' to C-11'), 28.1 (d, C-15, C-13'), 27.6 (t, C-8 to C-13, C-4' to C-11'), 26.0 (q, SiC($\underline{C}H_3)_3$), 25.0 (t, C-1), 23.5 (t, C-8 to C-13, C-4' to C-11'), 22.8 (q, C-16, C-17, C-14', C-15'), 18.1 (s, Si$\underline{C}(CH_3)_3$), 18.26, 18.21 (2q, SiCH($\underline{C}H_3)_2$), 12.5 (2d, Si$\underline{C}$H$(CH_3)_2$), −4.3, −5.0 (2q, Si($\underline{C}H_3)_2$) ppm.

(*2R,3R,6R*)-3-Hydroxy-2-((*R*)-2-hydroxy-13-methyltetradecanamido)-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yne-1-sulfonic acid (178)

exp: 144
DL752



According to GP 26, the reaction of thiol **SI-22** (20.0 mg, 20.3 µmol) with *m*-CPBA (11.7 mg, 40.7 µmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % NH_4OH, 90/10 → 0/100, eluting at 0/100), **178** as a colorless solid (0.52 mg, 3 %).

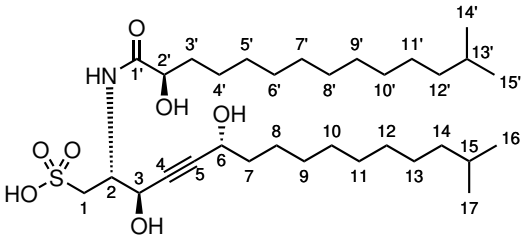
^{1}H-NMR (600 MHz**, MeOD):** δ = 4.74 (dd, J = 4.5, 1.4 Hz, 1 H, 3-H), 4.60 – 4.55 (m, 1 H, 6-H), 4.42 – 4.36 (m, 1 H, 2-H), 3.99 (dd, J = 8.4, 3.6 Hz, 1 H, 2'-H), 3.21 – 3.15 (m, 2 H, 1-H), 1.80 – 1.66 (m, 3 H, 3'-H, 7-H), 1.63 – 1.46 (m, 2 H, 3'-H), 1.45 – 1.24 (m, 32 H, 8-H to 13-H, 4'-H to 11'-H, 15-H, 13-H), 1.21 – 1.08 (m, 31 H, 14-H, 12'-H, SiCH($\underline{C}H_3)_2$, Si$\underline{C}$H$(CH_3)_2$), 0.88 (d, J = 6.7 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H) ppm.

^{13}C-NMR (151 MHz**, MeOD):** δ = 177.5 (s, C-1'), 88.7 (s, C-5), 83.5 (s, C-4), 73.1 (d, C-2'), 64.4 (d, C-3), 64.3 (d, C-6), 52.9 (d, C-2), 51.3 (t, C-1), 40.3 (t, C-14, C-12'), 40.1 (t, C-7), 35.6 (t, C-3'), 31.1, 30.9, 30.8, 30.7, 30.5 (5t, C-8 to C-13, C-4' to C-11'), 29.2 (d, C-14, C-12'), 28.6, 26.3 (2t, C-8 to C-13, C-4' to C-11'), 23.1 (q, C-16, C-17, C-14', C-15'), 18.6 (q, SiCH($\underline{C}H_3)_2$), 13.5 (d, Si$\underline{C}$H$(CH_3)_2$) ppm.

HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{41}H_{80}NO_7SSi$ 758.5419, found 758.5438.

(*2R,3R,6R*)-3,6-Dihydroxy-2-((*R*)-2-hydroxy-13-methyltetradecanamido)-15-methylhexadec-4-yne-1-sulfonic acid (179)

exp: 145
DL752



According to GP 26, the reaction of thiol **SI-22** (20.0 mg, 20.3 µmol) with *m*-CPBA (11.7 mg, 40.7 µmol) yielded, after flash chromatography (H_2O/MeOH + 0.1 % NH_4OH, 90/10 → 0/100, eluting at 5/95), **179** as a colorless solid (0.67 mg, 6 %, contains 8.2 equiv PPh_3O).

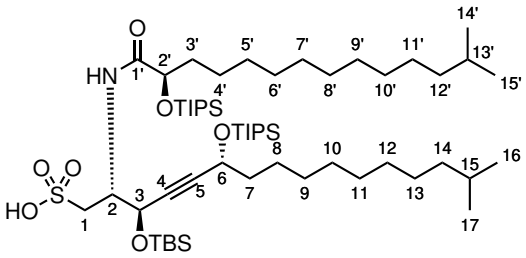
^{1}H-NMR (600 MHz**, MeOD):** δ = 4.73 (dd, J = 4.6, 1.5 Hz, 1 H, 3-H), 4.41 (dt, J = 8.2, 4.6 Hz, 1 H, 2'-H), 4.35 – 4.27 (m, 1 H, 6-H), 3.99 (dd, J = 8.5, 3.5 Hz, 1 H, 2-H), 3.26 – 3.14 (m, 2 H, 1-H), 1.82 – 1.74 (m, 1 H, 3'-H), 1.69 – 1.64 (m, 1 H, 3'-H), 1.61 – 1.21 (m, 27 H, 7-H to 13-H, 15-H, 4'-H to 11'-H, 13'-H), 1.21 – 1.06 (m, 10 H, 14-H, 12'-H), 0.88 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H) ppm.

^{13}C-NMR (151 MHz**, MeOD):** δ = 177.5 (s, C-1'), 88.6 (s, C-5), 82.2 (s, C-4), 73.1 (d, C-2'), 64.3 (d, C-3), 62.8 (d, C-6), 52.9 (d, C-2), 51.3 (t, C-1), 40.3 (t, C-14, C-12'), 39.0 (t, C-7) 35.5 (t, C-3'), 31.1, 30.85, 30.81, 30.7, 30.6 (5t, C-8 to C-13, C-4' to C-11'), 29.2 (d, C-14, C-12'), 28.7, 28.6, 26.5, 26.4 (4t, C-8 to C-13, C-4' to C-11'), 23.1 (q, C-16, C-17, C-14', C-15') ppm.

HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{32}H_{60}NO_7S$ 602.4085, found 602.4108.

(*2R,3R,6R*)-3-((*tert*-Butyldimethylsilyl)oxy)-15-methyl-2-((*R*)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamido)-6-((triisopropylsilyl)oxy)hexadec-4-yne-1-sulfonic acid (180)

exp: 146
DL773



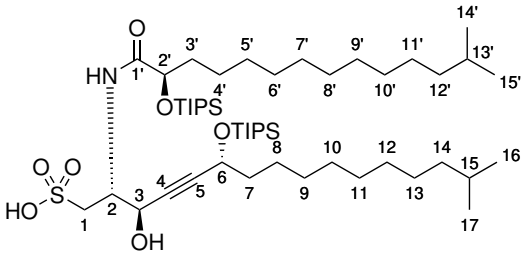
According to GP 26, the reaction of thioacetate **174** (38.0 mg, 37.1 µmol) with NaSMe (5.20 mg, 74.2 µmol), *m*-CPBA (73.1 mg, 296 µmol and DMSO (100 µL)) yielded, after flash chromatography (H_2O/MeOH + 0.1 % NH_4OH, 90/10 → 0/100, eluting at 0/100, followed by washing with *i*-PrOH), **180** as a colorless oil (10.0 mg, 29 %).

^{1}H-NMR (600 MHz**, MeOD):** δ = 7.13 (d, J = 9.6 Hz, 1 H, N-H), 5.21 (d, J = 3.4 Hz, 1 H, 3-H), 4.65 (tq, J = 7.9, 3.5 Hz, 1 H, 2-H), 4.61 – 4.54 (m, 1 H, 6-H), 4.34 (dd, J = 5.5, 3.5 Hz, 1 H, 2'-H), 3.13 (dd, J = 13.9, 9.3 Hz, 1 H, 1-H), 2.95 – 2.86 (m, 1 H, 1-H), 1.82 (tt, J = 12.6, 4.2 Hz, 1 H, 3'-H), 1.77 – 1.68 (m, 3 H, 7-H, 3'-H), 1.57 – 1.48 (m, 5 H, 8-H to 13-H, 4'-H to 11'-H, 15-H, 13-H), 1.45 – 1.22 (m, 46 H, 8-H to 13-H, 4'-H to 11'-H), 1.21 – 1.07 (m, 57 H, 14-H, 12'-H, SiCH($\underline{C}H_3)_2$, Si$\underline{C}$H$(CH_3)_2$), 0.91 (s, 9 H, SiC($C\underline{H_3})_3$), 0.88 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.18, 0.14 (2s, 2x 3 H, Si($C\underline{H_3})_2$) ppm.

^{13}C-NMR (151 MHz, MeOD): δ = 175.3 (s, C-1'), 89.5 (s, C-5), 82.8 (s, C-4), 75.0 (d, C-2'), 66.0 (d, C-3), 64.3 (d, C-6), 53.6 (t, C-1), 52.6 (d, C-2), 40.4 (t, C-7), 40.2 (t, C-14, C-12'), 36.6 (t, C-3'), 31.1, 30.9, 30.8, 30.6, 30.5 (5t, C-8 to C-13, C-4' to C-11'), 29.2 (d, C-15, C-13'), 28.6 (t, C-8 to C-13, C-4' to C-11'), 26.5 (q, SiC($\underline{C}H_3)_3$), 24.1, 23.7 (2t, C-8 to C-13, C-4' to C-11'), 23.1 (q, C-16, C-17, C-14', C-15'), 19.1 (s, Si$\underline{C}(CH_3)_3$), 18.75, 18.68 (2q, SiCH($\underline{C}H_3)_2$), 13.6, 13.5 (2d, Si$\underline{C}H(CH_3)_2$), −4.4, −4.7 (2q, Si($\underline{C}H_3)_2$) ppm.

(*2R,3R,6R*)-3-Hydroxy-2-((*R*)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamido)-15-methyl-6-((triisopropylsilyl)oxy)hexadec-4-yne-1-sulfonic acid (181)

exp: 147
DL781



According to GP 26, the reaction of thioacetate **174** (75.0 mg, 73.2 µmol) with NaSMe (10.3 mg, 147 µmol), *m*-CPBA (180 mg, 732 µmol) and Me_2S (267 µL, 3.66 mmol) yielded, after flash chromatography (cyclohexane/EtOAc + 0.1 % formic acid, 90/10 → 0/100, eluting at 0/100), **181** as a colorless solid (28.6 mg, 43 %).

^{1}H-NMR (500 MHz, MeOD): δ = 4.63 – 4.50 (m, 2 H, 2-H, 6-H), 4.38 (dd, J = 5.4, 3.6 Hz, 1 H, 2'-H), 3.15 (dd, J = 14.2, 6.3 Hz, 1 H, 1-H), 3.05 – 2.96 (m, 1 H, 1-H), 1.91 – 1.82 (m, 1 H, 3'-H), 1.77 – 1.68 (m, 3 H, 3'-H, 7-H), 1.57 – 1.47 (m, 5 H, 8-H to 13-H, 4'-H to 11'-H, 15-H, 13-H), 1.39 – 1.23 (m, 41 H, 8-H to 13-H, 4'-H to 11'-H), 1.23 – 1.08 (m, 56 H, 14-H, 12'-H, SiCH($\underline{C}H_3)_2$, Si$\underline{C}H(CH_3)_2$), 0.88 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H) ppm.

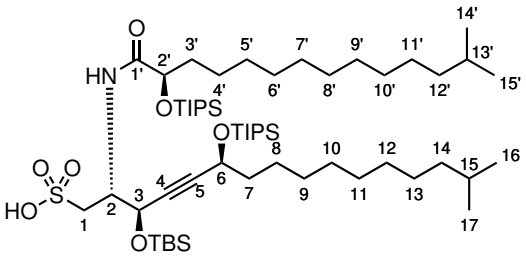
^{13}C-NMR (126 MHz, MeOD): δ = 176.0 (s, C-1'), 89.3 (s, C-5), 83.0 (s, C-4), 74.9 (d, C-2'), 64.6 (d, C-3), 64.4 (d, C-6), 53.0 (t, C-1), 52.1 (d, C-2), 40.3 (t, C-14, C-12'),36.5 (t, C-3'), 31.1, 30.9, 30.8, 30.77, 30.73, 30.62 (6t, C-8 to C-13, C-4' to C-11'), 29.2 (d, C-14, C-12'), 28.6, 24.1 (2t, C-8 to C-13, C-4' to C-11'), 23.1 (q, C-16, C-17, C-14', C-15'), 18.73, 18.67 (2q, SiCH($\underline{C}H_3)_2$), 13.5 (d, Si$\underline{C}H(CH_3)_2$) ppm.

IR (ATR) ν_{max}: 3464, 2923, 2865, 1644, 1463, 1217, 100, 1043 cm^{-1}.

$[\alpha]_D^{25}$**:** -1.47° (c = 1.0; $CHCl_3$).

(*2R,3R,6S*)-3-((*tert*-Butyldimethylsilyl)oxy)-15-methyl-2-((*R*)-13-methyl-2-((triisopropylsilyl)oxy)tetradecanamido)-6-((triisopropylsilyl)oxy)hexadec-4-yne-1-sulfonic acid (182)

exp: 148
DL790



According to GP 26, the reaction of thioacetate **175** (17.0 mg, 16.6 µmol) with NaSMe (2.33 mg, 33.2 µmol), *m*-CPBA (47.7 mg, 166 µmol) and Me_2S (60.6 µL, 829 µmol) yielded, after flash chromatography (cyclohexane/EtOAc + 0.1 % formic acid, 90/10 → 0/100, eluting at 0/100), **182** as a colorless oil (11.2 mg, 66 %).

^{1}H-NMR (500 MHz**, MeOD):** δ = 7.14 (d, J = 9.6 Hz, 1 H, N-H), 5.25 – 5.16 (m, 1 H, 3-H), 4.68 – 4.61 (m, 1 H, 2-H), 4.59 – 4.53 (m, 1 H, 6-H), 4.39 – 4.30 (m 1 H, 2'-H), 3.15 (dd, J = 13.8, 8.8 Hz, 1 H, 1-H), 2.92 (dd, J = 13.8, 4.1 Hz, 1 H, 1-H), 1.89 – 1.78 (m, 1 H, 3'-H), 1.78 – 1.68 (m, 3 H, 7-H, 3'-H), 1.65 – 1.46 (m, 5 H, 8-H to 13-H, 4'-H to 11'-H, 15-H, 13-H), 1.45 – 1.22 (m, 36 H, 8-H to 13-H, 4'-H to 11'-H), 1.22 – 1.08 (m, 46 H, 14-H, 12'-H, SiCH($\underline{C}H_3$)$_2$, Si$\underline{C}$H(CH_3)$_2$), 0.91 (s, 9 H, SiC($C\underline{H_3}$)$_3$), 0.88 (d, J = 6.6 Hz, 12 H, 16-H, 17-H, 14'-H, 15'-H), 0.17, 0.14 (2s, 2x 3 H, Si($C\underline{H_3}$)$_2$) ppm.

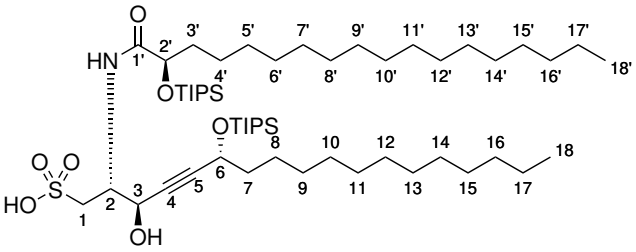
^{13}C-NMR (126 MHz**, MeOD):** δ = 175.4 (s, C-1'), 89.3 (s, C-5), 82.5 (s, C-4), 75.0 (d, C-2'), 66.0 (d, C-3), 64.4 (d, C-6), 53.5 (t, C-1), 52.6 (d, C-2), 40.4 (t, C-7), 40.3 (t, C-14, C-12'), 36.5 (t, C-3'), 31.1, 30.9, 30.8, 30.6, 30.5 (5t, C-8 to C-13, C-4' to C-11'), 29.2 (d, C-15, C-13'), 28.6 (t, C-8 to C-13, C-4' to C-11'), 26.5 (q, SiC($\underline{C}H_3$)$_3$), 24.1, (t, C-8 to C-13, C-4' to C-11'), 23.1 (q, C-16, C-17, C-14', C-15'), 19.0 (s, Si$\underline{C}$(CH_3)$_3$), 18.8, 18.7 (2q, SiCH($\underline{C}H_3$)$_2$), 13.6, 13.5 (2d, Si$\underline{C}$H(CH_3)$_2$), −4.5, −4.7 (2q, Si($\underline{C}H_3$)$_2$) ppm.

IR (ATR) ν_{max}: 3398, 2925, 2865, 1651, 1521, 1463, 1214, 1106, 1040 cm^{-1}.

$[\alpha]_D^{25}$**:** -12.0° (c = 2.0; $CHCl_3$).

(*2R,3R,6R*)-3-Hydroxy-6-((triisopropylsilyl)oxy)-2-((*R*)-2-((triisopropylsilyl)oxy)-octadecanamido)octadec-4-yne-1-sulfonic acid (183)

exp: 149
DL780



According to GP 26, the reaction of thioacetate **176** (35.0 mg, 32.4 µmol) with NaSMe (4.54 mg, 64.8 µmol), *m*-CPBA (79.8 mg, 324 µmol), Me_2S (118 µL, 1.62 mmol) yielded, after flash chromatography (cyclohexane/EtOAc + 1.0 % formic acid 90/10 → 0/100, eluting at 0/100), **183** as a colorless solid (9.2 mg, 29 %).

^{1}H-NMR (500 MHz**, MeOD):** δ = 7.94 (d, J = 7.8 Hz, 1 H, N-H), 4.92 (d, J = 4.1 Hz, 1 H, 3-H), 4.60 – 4.52 (m, 2 H, 2-H, 6-H), 4.36 (dd, J = 5.4, 3.6 Hz, 1 H, 2'-H), 3.13 (dd, J = 14.1, 6.7 Hz, 1 H, 1-H), 3.05 – 3.00 (m, 1 H, 1-H), 1.88 – 1.80 (m, 1 H, 3'-H), 1.77 – 1.68 (m, 3 H, 3'-H, 7-H), 1.57 – 1.47 (m, 3 H, 8-H to 17-H, 4'-H to 17'-H), 1.37 – 1.25 (m, 51 H, 8-H to 17-H, 4'-H to 17'-H), 1.23 – 1.04 (m, 40 H, SiCH($C\underline{H_3}$)$_2$, Si$\underline{C}$H(CH_3)$_2$), 0.90 (t, J = 6.9 Hz, 6 H, 18-H, 18'-H) ppm.

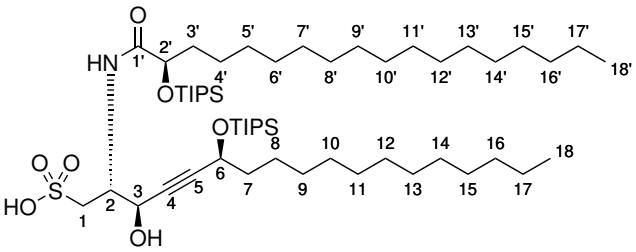
^{13}C-NMR (126 MHz**, MeOD):** δ = 176.0 (s, C-1'), 89.2 (s, C-5), 83.1 (s, C-4), 75.0 (d, C-2'), 64.6 (d, C-3), 64.4 (d, C-6), 53.1 (t, C-1), 52.3 (d, C-2), 40.3 (t, C-7), 36.6 (t, C-3'), 33.1, 30.83, 30.80, 30.74, 30.71, 30.68, 30.6, 30.5, 26.3, 24.2, 23.8 (11t, C-8 to C-17, C-4' to C-17'), 18.72, 18.66 (2q, SiCH($\underline{C}H_3$)$_2$), 14.5 (q, C-18, C-18'), 13.6 (d, Si$\underline{C}$H(CH_3)$_2$) ppm.

IR (ATR) ν_{max}: 3388, 2922, 2853, 1651, 1463, 1197, 1043 cm^{-1}.

$[\alpha]_D^{25}$**:** -9.62° (c = 1.0; $CHCl_3$).

(*2R,3R,6S*)-3-((*tert*-Butyldimethylsilyl)oxy)-6-((triisopropylsilyl)oxy)-2-((*R*)-2-(-(triisopropylsilyl)oxy)octadecanamido)octadec-4-yne-1-sulfonic acid (184)

exp: 150
DL779



According to GP 26, the reaction of thioacetate **177** (20.0 mg, 18.5 µmol) with NaSMe (2.50 mg, 37.0 µmol), *m*-CPBA (45.6 mg, 185 µmol), Me_2S (67.6 µL, 925 µmol) yielded, after flash chromatography (cyclohexane/EtOAc + 1.0 % formic acid 90/10 → 0/100, eluting at 0/100), **184** as a colorless solid (4.4 mg, 24 %).

^{1}H-NMR (500 MHz**, MeOD):** δ = 4.96 (dd, J = 4.6, 1.7 Hz, 1 H, 3-H), 4.61 – 4.52 (m, 2 H, 2-H, 6-H), 4.34 (dd, J = 5.5, 3.8 Hz, 1 H, 2'-H), 3.14 – 3.06 (m, 2 H, 1-H), 1.86 – 1.77 (m, 1 H, 3'-H), 1.76 – 1.69 (m, 3 H, 3'-H, 7-H), 1.69 – 1.56 (m, 1 H, 8-H to 17-H, 4'-H to 17'-H), 1.56 – 1.47 (m, 3 H, 8-H to 17-H, 4'-H to 17'-H), 1.37 – 1.27 (m, 67 H, 8-H to 17-H, 4'-H to 17'-H), 1.27 – 1.08 (m, 53 H, SiCH($C\underline{H}_3$)$_2$, Si$\underline{C}$H(CH_3)$_2$), 0.90 (t, J = 6.9 Hz, 12 H, 18-H, 18'-H) ppm.

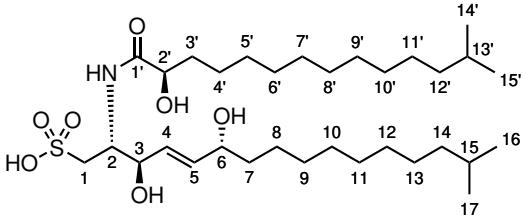
^{13}C-NMR (126 MHz**, MeOD):** δ = 175.9 (s, C-1'), 88.9 (s, C-5), 83.1 (s, C-4), 75.1 (d, C-2'), 64.5 (d, C-3), 64.4 (d, C-6), 53.0 (t, C-1), 52.4 (d, C-2), 40.3 (t, C-7), 36.7 (t, C-3'), 33.1, 30.74, 30.68, 30.6, 30.5 26.4, 24.3, 23.8 (8t, C-8 to C-17, C-4' to C-17'), 18.72, 18.66 (2q, SiCH($\underline{C}H_3$)$_2$), 14.5 (q, C-18, C-18'), 13.5 (d, Si$\underline{C}$H(CH_3)$_2$) ppm.

IR (ATR) ν_{max}: 3386, 2922, 2853, 1644, 1463, 1198, 1043 cm^{-1}.

$[\alpha]_D^{25}$**:** -26.1° (c = 0.32; $CHCl_3$).

(*2R,3R,6R,E*)-3,6-Dihydroxy-2-((*R*)-2-hydroxy-13-methyltetradecanamido)-15-methylhexadec-4-ene-1-sulfonic acid (186)

exp: 151
DL787

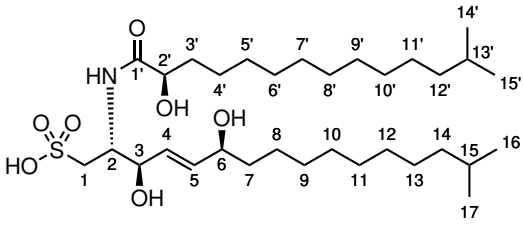


According to GP 27, the reaction of sulfonic acid **181** (28.0 mg, 30.6 µmol) with Red-Al® (247 µL, 764 µmol) and L-(+)-tartaric acid (458 mg, 3.05 mmol) yielded, after SPE and HPLC-purification (Phenomenex Luna Phenyl-Hexyl, 250 x 21.2 mm, H_2O/MeOH 40/60 → 0/100, eluting at 95/5), **186** as a colorless solid (1.10 mg, 5.9 %).

HRMS (ESI-TOF): calculated for [M − H]$^-$ $C_{32}H_{62}NO_7S$ 604.4252, found 604.4257.

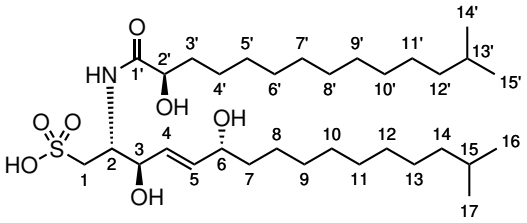
(*2R,3R,6S,E*)-3,6-Dihydroxy-2-((*R*)-2-hydroxy-13-methyltetradecanamido)-15-methylhexadec-4-ene-1-sulfonic acid (187)

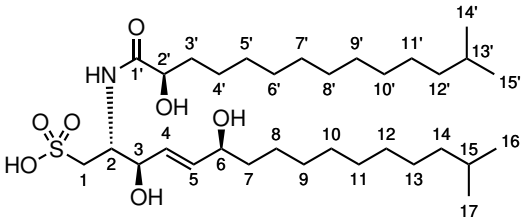
exp: 152
DL791/
DL793



According to GP 27, the reaction of sulfonic acid **182** (11.0 mg, 10.7 µmol) with Red-Al® (86.4 µL, 267 µmol) and L-(+)-tartaric acid (80.1 mg, 534 µmol) yielded, after SPE-purification (equilibrate: 60 % MeOH in H_2O + 0.1 % NH_4OH; elute: 100 % MeOH + 0.1 % NH_4OH), a colorless solid, which contained a mixture of differently protected sulfonic acids. The crude was then dissolved in THF (456 µL), and a solution of TBAF in THF (183 µL, 183 µmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h, diluted with H_2O and subjected to SPE-purification (equilibrate: 60 % MeOH in H_2O + 0.1 % NH_4OH; elute: 100 % MeOH + 0.1 % NH_4OH) to yield **187** as a colorless solid (0.99 mg, 2 %).

Table 4.2: Comparative ^{1}H-NMR and ^{13}C-NMR (DMSO−d_6) analysis of isolated sulfonolipid **RIF-2** (m/z 604.425 [M−H]$^-$) from *A. machipongonensis* PR1 and synthetic compounds **186** and **187**.



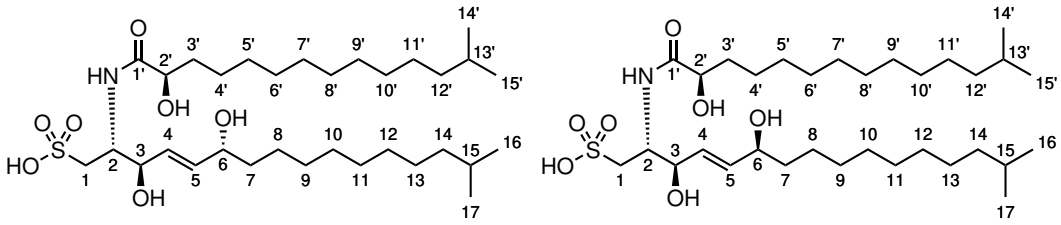


	^{1}H-NMR (600 MHz)					^{13}C-NMR (150 MHz)				
Pos.	**4**	**186** (NH_4^+ salt)		**187** (NBu_4^+ salt)		**4**	**186** (NH_4^+ salt)		**187** (NBu_4^+ salt)	
	δ_H mult. (J in Hz)	δ_H [a]	$\Delta\delta_H$	δ_H [a]	$\Delta\delta_H$ [c]	δ_C [a] mult.	δ_C [a]	$\Delta\delta_C$ [c]	δ_C [a,b]	$\Delta\delta_C$ [c]
1	2.57 dd (14.1, 4.6)	2.58	0.01	2.58 [b]	0.01	51.03 t	51.04	0.01	51.09	0.06
	2.86 dd (14.1, 6.1)	2.85	-0.01	2.90	0.04					
1'	–	–	–	–	–	173.7 s	173.7	0.0	n.a.	n.a.
2	3.94 m	3.94	0.00	3.96	0.02	50.98 d	50.98	0.0	50.66	-0.32
2'	3.74 m	3.75	0.01	3.74	0.00	71.0 d	71.0	0.0	71.0	0.0
2'-OH	5.48 d (5.2)	5.48	0.00	5.53	0.05	-	-	-	-	-
3	4.23 m	4.23	0.00	4.24	0.02	71.5 d	71.6	0.1	71.4	-0.1
3-OH	5.24 d (5.2)	5.23	-0.01	5.21	-0.03	-	-	-	-	-
3'	1.40 m	1.40	0.00	-1.40	0.00	34.4 t	34.4	0.0	n.a.	n.a.
	1.57 m	1.57	0.00	-1.57	0.00					
4	5.52 dd (15.6, 5.4)	5.50	-0.02	5.46	-0.06	129.1 d	129.1	0.0	129.3	0.2

Pos.	^{1}H-NMR (600 MHz)					^{13}C-NMR (150 MHz)				
	4	**186** (NH_4^+ salt)		**187** (NBu_4^+ salt)		**4**	**186** (NH_4^+ salt)		**187** (NBu_4^+ salt)	
	δ_H mult. (J in Hz)	δ_H[a]	$\Delta\delta_H$	δ_H[a]	$\Delta\delta_H$[c]	δ_C[a] mult.	δ_C[a]	$\Delta\delta_C$[c]	δ_C[a,b]	$\Delta\delta_C$[c]
5	5.58 dd (15.6, 6.0)	5.58	0.00	5.53	0.05	134.7 d	134.7	0.0	134.6	-0.1
6	3.85 m	3.85	0.00	3.82	-0.03	70.3 d	70.4	0.1	70.6	0.3
6-OH	4.50 d (4.8)	4.52	0.02	4.56	0.06	-	-	-	-	-
7		1.34-1.30 br. m				37.2 t				
8-13, 4'-11'		1.27-1.17 br. m				30.0-24.7 7t				
14, 12'		1.16-1.11 br. m				38.5 t				
15, 13'		1.49 br. m				27.4 d				
14', 15', 16, 17		0.84 d (6.6)				22.5 q				
NH	8.02 d (8.1)	7.99	-0.03	8.04	0.02	-	-	-	-	-

[a] All values in ppm; [b] according to HSQC-data; [c] difference to isolated compound **4**;
[n.a.] not unambigously assigned.

Table 4.3: Comparative ^{1}H-NMR and ^{13}C-NMR ($MeOD_4$) analysis of isolated sulfonolipid **RIF-2** (m/z 604.425 $[M-H]^-$) from *A. machipongonensis* PR1 and synthetic compounds **186** and **187**.

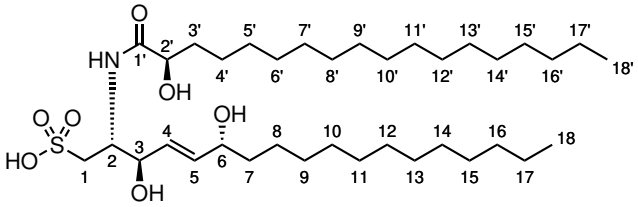


	^{1}H-NMR (600 MHz)					^{13}C-NMR (150 MHz)				
Pos.	**4**	**186** (NH_4^+ salt)		**187** (NBu_4^+ salt)		**4**	**186** (NH_4^+ salt)		**187** (NBu_4^+ salt)	
	δ_H mult. (J in Hz)	δ_H[a]	$\Delta\delta_H$	δ_H[a]	$\Delta\delta_H$[c]	δ_C[a] mult.	δ_C[a]	$\Delta\delta_C$[c]	δ_C[a,b]	$\Delta\delta_C$[c]
1	3.07 dd (14.4, 3.8)	3.08	0.01	3.10	0.03	51.2 t	51.3	0.1	51.1	-0.1
	3.15 dd (14.4, 8.2)	3.13	-0.02	3.17	0.02					
1'	–	–	–	–	–	177.3 s	177.3	0.0	n.a.	n.a.
2	4.29 dd (8.4, 4.3)	4.30	0.01	4.28	-0.01	52.5 d	52.4	-0.1	52.4	-0.1
2'	3.98 dd (8.4, 4.3)	3.99	0.01	3.98	0.00	73.1 d	73.0	-0.1	73.0	-0.1
3	4.38 t (5.5)	4.35	-0.03	4.35	-0.03	73.8 d	73.8	0.0	73.2	-0.6
4	5.68 ddd (15.6, 5.4, 1.0)	5.68	0.00	5.67	-0.01	130.3 d	130.2	-0.1	130.4	0.1
5	5.80 ddd (15.6, 6.0, 1.2)	5.80	0.00	5.77	-0.03	136.8 d	136.9	0.1	137.0	0.2
6	4.04 dd (8.5, 3.6)	4.04	0.00	4.02	-0.02	72.9 d	72.9	0.0	73.0	0.1
7	1.44-1.40 br. m					38.3 t				
8-13, 3'-11'	1.57-1.16 br. m					35.5-26.4 8t				
14, 12'	1.13-1.08 br. m					40.3 t				
15, 13'	1.46 br. m					29.1 d				
14', 15', 16, 17	0.88 d (6.6)					23.0 q				

[a] All values in ppm; [b] according to HSQC-data; [c] difference to isolated compound **4**;
[n.a.] not unambigously assigned.

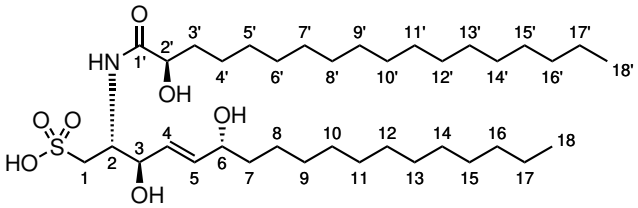
(*2R,3R,6R,E*)-3,6-Dihydroxy-2-((*R*)-2-hydroxy-octadecanamido)-octadec-4-ene-1-sulfonic acid (188)

exp: 153
DL789



According to GP 27, the reaction of sulfonic acid **183** (9.2 mg, 9.47 µmol) with Red-Al® (30.0 µL, 93.8 µmol) and L-(+)-tartaric acid (146 mg, 947 µmol) yielded, after SPE and HPLC-purification (Phenomenex Luna Phenyl-Hexyl, 250 x 21.2 mm, H_2O/MeOH 40/60 → 0/100, eluting at 95/5), **188** as a colorless solid (0.90 mg, 6.1 %).

Table 4.4: ^{1}H-NMR and ^{13}C-NMR-data for sulfonolipid **188**.



Pos.	^{1}H-NMR (600 MHz)		^{13}C-NMR (150 MHz)[b]	
	δ_{MeOD_4}[a]	δ_{DMSO-d_6}[a]	δ_{MeOD_4}[a]	δ_{DMSO-d_6}[a]
	mult. (J in Hz)	mult. (J in Hz)	mult.	mult.
1	3.07	2.52[b]	50.7	50.7
	3.15	2.86		
1'	–	–	n.a.	n.a.
2	4.29	3.93	52.2	51.1
2'	4.04	3.74	72.6	70.8
3	4.38	4.23	73.6	71.4
4	5.68	5.50	131.0	129.1
5	5.80	5.58	135.6	134.4
6	3.98	3.85	73.0	70.4
7–17, 3'–17'	1.74 – 1.22	1.49 – 1.17	30.4	28.8, 21.7
18, 18'	0.93 – 0.88	0.90-0.80	14.3	13.6
N-H	–	8.02	–	–

[a] All values in ppm; [b] according to HSQC-data;
[n.a.] not unambigously assigned.

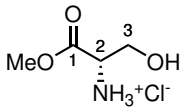
HRMS (ESI-TOF): calculated for $[M - H]^-$ $C_{36}H_{70}NO_7S$ 660.4878, found 660.4877.

4.8 Projects related to the synthesis of other natural products

4.8.1 Synthesis of serine amide derivatives

(*S*)-3-Hydroxy-1-methoxy-1-oxopropan-2-aminium chloride (191)

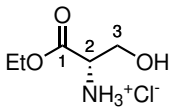
exp: 154
DL249



Acetyl chloride (50.9 mL, 714 mmol) was added dropwise to MeOH (240 mL) at 0 °C and, after stirring for 5 min, L-serine (26.2 g, 249 mmol) was added. The mixture was refluxed for 1 h and after cooling to r.t., the volatiles were removed *in vacuo* to yield **191** as a colorless solid (38.2 g, 99 %).

(*S*)-3-Hydroxy-1-ethoxy-1-oxopropan-2-aminium chloride (192)

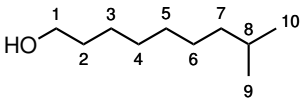
exp: 155
PS008



Thionyl chloride (70.7 mL, 105 mmol) was added dropwise to EtOH (200 mL) at −10 °C and, after stirring for 10 min, L-serine (10.0 g, 95 mmol) was added. The mixture was refluxed for 2 h and concentrated *in vacuo* after cooling to r.t. Precipitation with cyclohexane yielded **192** as a colorless solid (73.8 g, 86 %).

8-Methylnonan-1-ol (SI-23)

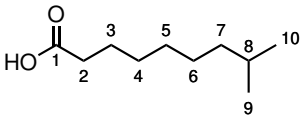
exp: 156
DL160



According to GP 1, the reaction of 6-bromohexan-1-ol (5.00 g, 27.6 mmol) with *i*-butylmagnesium bromide (34.5 mL, 69.0 mmol) and Li_2CuCl_4 (4.00 mL, 400 µmol) yielded **SI-23** as a colorless oil (4.90 g, quant.). The product was used without further purification.

8-Methylnonanoic acid (193)

exp: 157
DL164



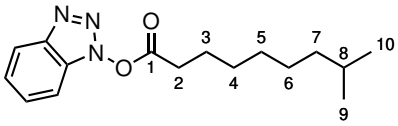
According to GP 2, the reaction of alcohol **SI-23** (4.30 g, 27.6 mmol) with $KMnO_4$ (42.9 g, 272 mmol) and NaOH (16.3 g, 407 mmol) yielded **193** as a yellowish liquid (4.67 g, 99 %).

^{1}**H-NMR (**300 MHz**, CDCl$_3$):** δ = 2.35 (t, J = 7.5 Hz, 2 H, 2-H), 1.73 – 1.58 (m, 2 H, 3-H), 1.50 (hept, J = 6.6 Hz, 1 H, 8-H), 1.41 – 1.21 (m, 6 H, 4-H to 6-H), 1.21 – 1.09 (m, 2 H, 7-H), 0.86 (d, J = 6.6 Hz, 6 H, 9-H, 10-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 180.8 (s, C-1), 39.2 (t, C-7), 34.3 (t, C-2), 29.6, 29.2 (2t, C-3 to C-6), 28.1 (d, C-8), 27.3, 24.8 (2t, C-3 to C-6), 22.8 (q, C-9, C-10) ppm.

1*H*-Benzo[d][1,2,3]triazol-1-yl 8-methylnonanoate (194)

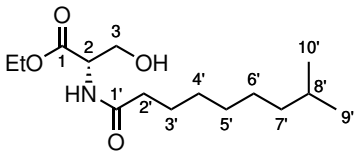
exp: 158
DL183



EDC (1.30 g, 6.78 mmol) and HOBt·H_2O (1.10 g, 7.18 mmol) were added to a solution of carboxylic acid **193** (1.00 g, 5.80 mmol) in CH_2Cl_2 (25.8 mL) and the mixture was stirred at r.t. for 10 h. NH_4Cl solution was added, the aqueous phase extracted with CH_2Cl_2 (3x), the combined organic phase washed with sat. $NaHCO_3$ solution, brine and dried over $MgSO_4$. The extract was filtered and the volatiles removed *in vacuo* to yield **194** as a colorless solid (1.52 g, 91 %), which was directly used in the next step without further purification.

Ethyl (8-methylnonanoyl)-L-serinate (195)

exp: 159
DL195



DIPEA (300 µL, 1.77 mmol) was added to a suspension of L-serine ethyl ester hydrochloride (100 mg, 589 µmol) in CH_2Cl_2 (2.95 mL) and the mixture stirred at r.t. for 30 min. The reaction was cooled to 0 °C, HOBt-ester **194** (187 mg, 649 µmol) was added and the suspension stirred at 4 °C for 16 h. Sat. NH_4Cl solution was added, the aqueous phase extracted with EtOAc (3x), the combined organic phase was washed with Na_2CO_3 solution, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc + 0.5 % Et_3N 50/50) to yield **195** as a colorless solid (67.2 mg, 40 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.60 (d, J = 7.5 Hz, 1 H, N-H), 4.61 (dt, J = 7.5, 3.7 Hz, 1 H, 2-H), 4.21 (q, J = 7.1 Hz, 2 H, $OC\underline{H_2}CH_3$), 3.90 (qd, J = 11.2, 3.7 Hz, 2 H, 1-H), 3.23 (s, 1 H, O-H), 2.29 – 2.18 (m, 2 H, 2'-H), 1.67 – 1.37 (m, 3 H, 3'-H, 8'-H), 1.37 – 1.19 (m, 10 H, 4'-H to 6'-H, $OCH_2C\underline{H_3}$), 1.18 – 1.05 (m, 2 H, 7'-H), 0.83 (d, J = 6.6 Hz, 6 H, 9'-H, 10'-H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 173.9 (s, C-1'), 170.6 (s, C-1), 64.2 (t, C-3), 62.2 (t, $O\underline{C}H_2CH_3$), 55.1 (d, C-2), 39.1 (t, C-7'), 36.7 (t, C-2'), 29.7, 29.4 (2t, C-3' to C-6'), 28.1 (d, C-8'), 27.4, 25.7 (2t, C-3' to C-6'), 22.8 (q, C-9', C-10'), 14.3 (q, $OCH_2\underline{C}H_3$) ppm.

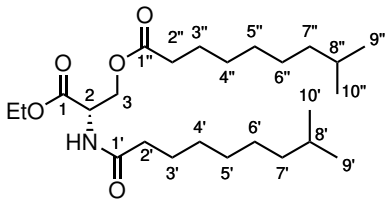
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{15}H_{30}NO_4$ 288.2169, found 288.2164.

IR (ATR): ν_{max} = 2926, 2855, 1746, 1652, 1540, 1456, 1218 cm^{-1}.

$[\alpha]_D^{25}$**:** +21.8° (c = 0.18; $CHCl_3$).

(*S*)-3-Ethoxy-2-(8-methylnonanamido)-3-oxopropyl 8-methylnonanoate (196)

exp: 160
DL205

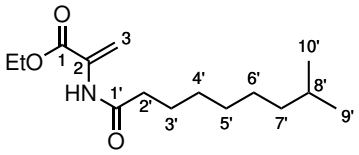


DIPEA (836 µL, 5.06 mmol) was added to a suspension of L-serine ethyl ester hydrochloride (350 mg, 2.06 mmol) in CH_2Cl_2 (10.3 mL) and the mixture stirred at r.t. for 30 min. The reaction was cooled to 0 °C, HOBt-ester **194** (1.19 g, 4.12 mmol) was added and the suspension stirred at 4 °C for 16 h. Sat. NH_4Cl solution was added, the aqueous phase extracted with EtOAc (3x), the combined organic phase washed with Na_2CO_3 solution, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (cyclohexane/EtOAc + 0.5 % Et_3N 50/50) to yield **195** as a colorless solid (189 mg, 40 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.24 – 6.19 (m, 1 H, N-H), 4.87 – 4.78 (m, 1 H, 2-H), 4.46 (ddd, J = 11.3, 4.0, 1.6 Hz, 1 H, 1-H), 4.37 – 4.29 (m, 1 H, 1-H), 4.20 (q, J = 7.1 Hz, 2 H, $OC\underline{H_2}CH_3$), 2.27, 2.22 (2t, J = 7.5 Hz, 2x 2 H, 2'-H, 2"-H), 1.68 – 1.53 (m, 4 H, 3'-H, 3"-H), 1.53 – 1.43 (m, 2 H, 8'-H, 8"-H), 1.34 – 1.21 (m, 14 H, 4'-H to 6'-H, 4"-H to 6"-H, $OCH_2C\underline{H_3}$), 1.20 – 1.09 (m, 4 H, 7'-H, 7"-H) 0.84 (d, J = 6.7 Hz, 12 H, 9'-H, 10'-H, 9"-H, 10"-H) ppm.

Ethyl 2-(8-methylnonanamido)acrylate (198)

exp: 161
DL204

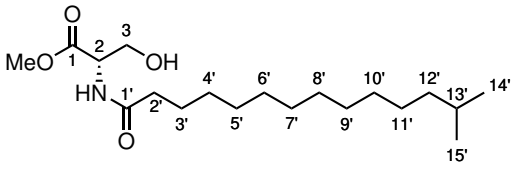


Imidazole (6.16 mg, 90.5 µmol) was added to a solution of PPh_3 (23.7 mg, 90.5 µmol) in CH_2Cl_2 (302 µL) and the mixture stirred at r.t. until all imidazole was dissolved. The solution was cooled to 0 °C, I_2 (23.0 mg, 90.5 µmol) was added and the reaction turned brown. After stirring for 15 min at r.t., alcohol **195** (14.0 mg, 48.7 µmol) in CH_2Cl_2 (138 µL) was added and the reaction stirred in the dark at r.t. for 5 h. The mixture was then filtered over a small pad of silica, the volatiles were removed *in vacuo* and the residue purified by flash chromatography (cyclohexane/EtOAc + 0.5 % Et_3N 20/1) to yield **198** as a yellowish oil (7.70 mg, 59 %).

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.83 – 7.63 (m, 1 H, N-H) 6.60 (s, 1 H, 3-H), 5.87 (s, 1 H, 3-H), 4.29 (q, J = 7.1 Hz, 2 H, $OC\underline{H_2}CH_3$), 2.31 (t, J = 7.6 Hz, 2 H, 2'-H), 1.67 (p, J = 7.5 Hz, 2 H, 3'-H), 1.55 – 1.47 (m, 1 H, 8'-H), 1.34 (t, J = 7.1 Hz, 3 H, $OCH_2C\underline{H_3}$), 1.32 – 1.23 (m, 8 H, 4'-H to 6'-H), 1.19 – 1.11 (m, 2 H, 7'-H), 0.86 (d, J = 6.6 Hz, 6 H, 9'-H, 10'-H) ppm.

Methyl (13-methyltetradecanoyl)-L-serinate (200)

exp: 162
DL255



EDC (4.62 g, 24.1 mmol) and HOBt·H_2O (4.92 g, 32.1 mmol) were added to a solution of carboxylic acid **34** (5.06 g, 20.9 mmol) in CH_2Cl_2 (52.2 mL) and the reaction stirred at r.t. for 30 min. The mixture was added to a solution of L-serine ethyl ester hydrochloride (1.00 g, 6.43 mmol) and DIPEA (5.47 mL, 32.14 mmol) in CH_2Cl_2 (16.1 mL) and stirred at r.t. for 72 h. Sat. NH_4Cl solution was added, the aqueous phase extracted with CH_2Cl_2, the combined organic phase washed with sat. Na_2CO_3 solution, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (CH_2Cl_2/*i*-PrOH 20/1) to yield **200** as a colorless solid (2.64 g, 48 %).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.40 (d, J = 7.1 Hz, 1 H, N-H), 4.69 (dt, J = 7.3, 3.7 Hz, 1 H, 2-H), 3.95 (dd, J = 6.3, 3.7 Hz, 2 H, 3-H), 3.79 (s, 3 H, OC$\underline{H_3}$), 2.33 – 2.15 (m, 2 H, 2'-H), 1.65 (p, J = 7.3 Hz, 2 H, 3'-H), 1.59 – 1.43 (m, 1 H, 13'-H), 1.35 – 1.20 (m, 20 H, 4'-H to 11'-H), 1.20 – 1.04 (m, 2 H, 12'-H), 0.86 (d, J = 6.6 Hz, 6 H, 14'-H, 15'-H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 174.0 (s, C-1'), 171.2 (s, C-1), 63.5 (t, C-3), 54.7 (d, C-2), 52.8 (q, O$\underline{C}H_3$), 39.1 (t, C-12'), 36.6 (t, C-2'), 30.0, 29.81, 29.76, 29.7, 29.6, 29.5, 29.3 (7t, C-3' to C-11'), 28.1 (d, C-13'), 27.5, 25.7 (C-3' to C-11'), 22.8 (q, C-14', C-15') ppm.

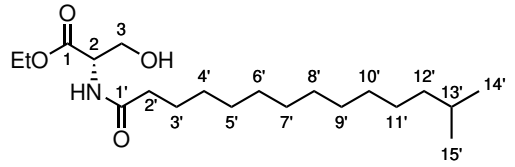
HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{19}H_{38}NO_4$ 344.2795, found 344.2787.

IR (ATR): ν_{max} = 3293, 2951, 2917, 2849, 1734, 1639, 1548, 1469, 1237, 1080 cm^{-1}.

$[\alpha]_D^{25}$**:** +13.8° (c = 1.0; $CHCl_3$).

Ethyl (13-methyltetradecanoyl)-L-serinate (201)

exp: 163
DL251



EDC (1.85 g, 9.64 mmol) and HOBt·H_2O (1.97 g, 12.7 mmol) were added to a solution of carboxylic acid **34** (2.03 g, 8.36 mmol) in CH_2Cl_2 (20.9 mL) and the reaction stirred at r.t. for 30 min. The mixture was added to a solution of L-serine methyl ester hydrochloride (2.50 g, 16.1 mmol) and DIPEA (13.7 mL, 80.4 mmol) in CH_2Cl_2 (40.2 mL) and stirred at r.t. for 72 h. Sat. NH_4Cl solution was added, the aqueous phase extracted with CH_2Cl_2, the combined organic phase washed with sat. Na_2CO_3 solution, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (CH_2Cl_2/*i*-PrOH 20/1) to yield **201** as a colorless solid (1.49 g, 65 %).

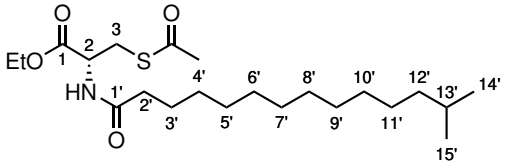
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.38 (d, J = 7.0 Hz, 1 H, N-H), 4.66 (dt, J = 7.3, 3.8 Hz, 1 H, 2-H), 4.25 (q, J = 7.1 Hz, 2 H, OC$\underline{H_2}$CH$_3$), 3.95 (dd, J = 3.8, 2.2 Hz, 2 H, 3-H), 2.33 – 2.22 (m, 2 H, 2'-H), 1.65 (p, J = 7.6 Hz, 2 H, 3'-H), 1.51 (hept, J = 6.6 Hz, 1 H, 13'-H), 1.37 – 1.21 (m, 19 H, 4'-H11', OCH$_2$C$\underline{H_3}$), 1.19 – 1.11 (m, 2 H, 12'-H), 0.86 (d, J = 6.6 Hz, 6 H, 14'-H, 15'-H) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$): δ = 173.9 (s, C-1'), 170.7 (s, C-1), 63.9 (t, C-3), 62.1 (t, O<u>C</u>H$_2$CH$_3$), 55.0 (d, C-2), 39.2 (t, C-12'), 36.7 (t, C-3'), 30.1, 29.84, 29.79, 29.75, 29.6, 29.5, 29.4 (7t, C-5' to C-11'), 28.1 (d, C-13'), 27.5 (t, C-5' to C-11'), 25.7 (t, C-4'), 22.8 (q, C-14', C-15'), 14.3 (q, OCH$_2$<u>C</u>H$_3$) ppm.

IR (ATR): ν_{max} = 3331, 2913, 2847, 1739, 1725, 1640, 1615, 1540, 1465, 1382, 1303, 1196, 1136 cm^{-1}.

Ethyl *S*-acetyl-*N*-(13-methyltetradecanoyl)-L-cysteinate (SI-24)

exp: 164
DL217



According to GP 25, the reaction of alcohol **201** (20.0 mg, 55.9 µmol) with PPh_3 (17.6 mg, 67.1 µmol), DIAD (14.7 mg, 72.7 µmol) and thioacetic acid (8.03 µL, 112 µmol) yielded, after flash chromatography (cyclohexane/EtOAc 4/1 → 3/2, eluting at 2/1), **SI-24** as a yellowish oil (6.5 mg, 28 %).

^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.20 (d, J = 7.6 Hz, 1 H, N-H), 4.78 (dt, J = 7.4, 5.4 Hz, 1 H, 2-H), 4.20 (q, J = 7.2 Hz, 2 H, OC<u>H$_2$</u>CH$_3$), 3.38 (dd, J = 5.4, 2.2 Hz, 2 H, 3-H), 2.34 (s, 3 H, SCOC<u>H$_3$</u>), 2.24 – 2.15 (m, 2 H, 2'-H), 1.61 (p, J = 7.4 Hz, 2 H, 3'-H), 1.51 (hept, J = 6.7 Hz, 1 H, 13'-H), 1.32 – 1.22 (m, 23 H, 4'-H to 11'-H, OCH$_2$C<u>H$_3$</u>), 1.17 – 1.12 (m, 2 H, 12'-H), 0.86 (d, J = 6.6 Hz, 6 H, 14'-H, 15'-H) ppm.

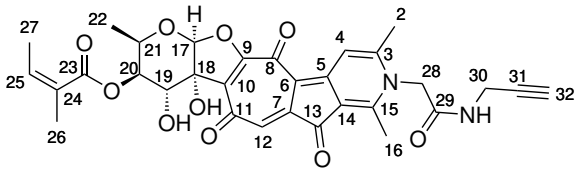
^{13}C-NMR (151 MHz, $CDCl_3$): δ = 195.4 (s, S<u>C</u>OCH$_3$), 173.1 (s, C-1'), 170.4 (s, C-1), 62.2 (t, O<u>C</u>H$_2$CH$_3$), 52.1 (d, C-2), 39.2 (t, C-12'), 36.6 (t, C-2'), 31.1 (t, C-3), 30.6 (q, SCO<u>C</u>H$_3$), 30.1, 29.9, 29.81, 29.77, 29.6, 29.5, 29.3 (7t, C-4' to C-11'), 28.1 (d, C-13'), 27.6 (t, C-4' to C-11'), 25.6 (t, C-3'), 22.8 (q, C-14, C-15'), 14.2 (q, OCH$_2$<u>C</u>H$_3$) ppm.

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{22}H_{42}O_4NS$ 416.2829, found 416.2822.

4.8.2 Derivatization of rubterolones

Propargyl-rubterolone (203)

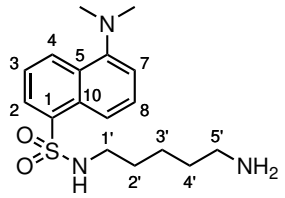
exp: 165
DL394



A stock solution of propargylic amine (20 µL of a 2.3 M solution in DMF, 45.2 µmol) and COMU (1.5 mg, 3.6 µmol) was added to a deep green solution of rubterolone D (**202**, 1.0 mg, 1.81 µmol) in DMF (70 µL) at 3 °C. The mixture was shaken below 5 °C and the reaction progress monitored *via* TLC ($CHCl_3$/ MeOH/ AcOH 75/25/1). Additional COMU (1.5 mg, 3.6 µmol) was added every 30 min and propargylic amine (20 µL, 45.2 µmol) every 60 min. The reaction mixture was concentrated *in vacuo* upon completion or after 3 h and purified by RP-HPLC (Phenomonex C18(2) 250 x 10 mm; H_2O + 0.1 % formic acid/MeCN; 60/40 → 0/100; eluting at 40/60) to yield propargyl-rubterolone D **203** as a deep red solid (0.1 mg, 10 %).

N-(5-Aminopentyl)-5-(dimethylamino)naphthalene-1-sulfonamide (SI-25)

exp: 166
DL386



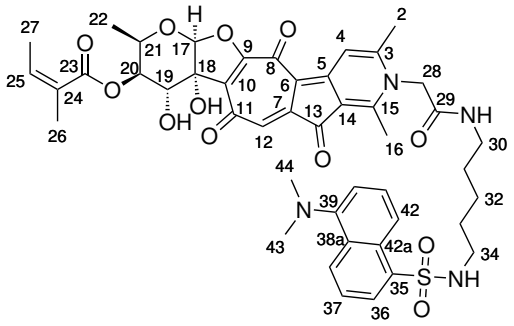
A solution of dansyl chloride (100 mg, 370 µmol) in CH_2Cl_2 was added dropwise to a solution of pentane-1,5-diamine (433 µL, 3.71 mmol) in CH_2Cl_2 (926 µL) and the mixture stirred at r.t. for 6 h. After addition of H_2O, the phases were separated, the organic phase was washed with Na_2CO_3 solution, brine and dried over $MgSO_4$. The extract was filtered, the volatiles removed *in vacuo* and the crude product purified by flash chromatography (H_2O/MeOH + 0.1 % formic acid 90/10 → 0/100, eluting at 85/15) to yield **SI-25** as a greenish oil.

^{1}H-NMR (600 MHz**, MeOD$_4$):** δ = 8.55 (d, J = 8.6 Hz, 1 H, 4-H), 8.51 – 8.32, 8.27 – 8.21 (2m, 2x 1 H, 2-H, 9-H), 7.75 – 7.61 (m, 2 H, 3-H, 8-H), 7.45 (q, J = 7.1, 6.6 Hz, 1 H, 7-H), 3.06 – 2.96 (m, 6 H, N($\underline{CH_3}$)$_2$) 2.86 (t, J = 6.9 Hz, 2 H, 1'-H), 2.80 (t, J = 7.7 Hz, 2 H, 5'-H), 1.53 (p, J = 7.9 Hz, 2 H, 2'-H), 1.45 (p, J = 7.0 Hz, 2 H, 4'-H), 1.37 – 1.22 (m, 2 H, 3'-H) ppm.

^{13}C-NMR (151 MHz**, MeOD):** δ = 151.3 (s, C-6), 137.4 (s, C-10), 130.9 (s, C-5), 130.6, 130.4, 130.2, 129.0, 124.9, 121.7, 117.1 (s + 6d, C-1 to C-4, C-7 to C-9), 46.1 (q, N($\underline{CH_3}$)$_2$), 43.4 (C-1'), 40.5 (t, C-5'), 30.2 (t, C-2'), 28.0 (t, C-4'), 24.3 (t, C-3') ppm.

Dansyl-cadaverinylrubterolone (204)

exp: 167
DL417



A solution of HATU (6.0 mg, 16 µmol) in DMF (20 µL) was added to rubterolone D (**202**, 1.0 mg, 1.81 µmol) at r.t. and the deep green solution cooled to 8 °C. DIPEA (3.4 µL, 20 µmol) and dansyl cadaverine **SI-25** (3.3 mg, 10 µmol) in DMF (30 µL) were added and the mixture shaken at 22 °C → 35 °C for 3.5 h. The crude was directly purified by HPLC (Phenomonex Phenyl-Hexyl 250 x 10 mm; H_2O + 0.1 % formic acid/MeCN; 50/50 → 0/100; eluting at 40/60) to yield compound **204** as a deep red solid (0.96 mg, 61 %).

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{45}H_{51}O_{12}N_4S$ 871.3219, found 871.3214.

Table 4.5: ^{1}H-NMR (600 MHz) and ^{13}C-NMR (150 MHz) data for rubterolone **204**.

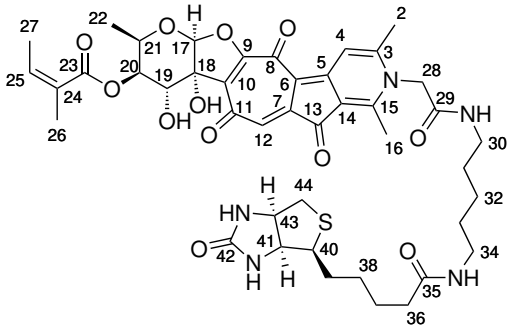
Pos.	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)	**Pos.**	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)
1				26	11.67 q	1.57	t (1.1)
2	21.91 q	2.56	s	27	13.86 q	1.43	dd (7.1, 1.1)
3	157.76 s			28	51.50 d	4.96	br. s
4	115.90 d	8.40	s	29	164.29 s		
5	160.34 s			30	38.75 t	2.98	dd (13.2, 7.2)
6	109.75 s			31	28.15 t	1.26	m
7	136.75 s			32	23.22 t	1.15	m
8	170.06 s			33	28.66 t	1.31	m
9	163.76 s			34	42.24 t	2.76	m
10	126.00 s			35	129.04 s		
11	183.00 s			36	128.18 d	8.09	dd (7.4, 1.2)
12	118.43 d	6.23	s	37	123.57 d	7.62	dd (8.4, 7.5)
13	193.53 s			38	129.32 d	8.45	d (8.5)
14	121.26 s			38a	129.08 s		
15	152.00 s			39	151.33 s		
16	13.86 q	2.76	s	40	115.10 d	7.26	d (7.4)
17	102.83 d	5.35	s	41	127.77 d	7.59	t (8.5)
18	80.10 s			42	119.13 d	8.30	d (8.7)
19	64.08 d	5.08	t (4.0)	42a	136.12 s		

Pos.	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)	Pos.	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)
20	71.67 d	4.70	dd (4.2, 1.2)	43	45.05 q	2.82	s
21	64.39 d	4.24	q (6.2)	44	45.05 q	2.82	s
22	15.93 q	0.98	d (6.5)	NH(1)		8.44	br. s
23	165.86 s			NH(2)		7.86	t (5.9)
24	127.44 s			19-OH		5.78	d (4.3)
25	137.36 d	6.35	qd (6.4, 1.4)				

[a] All values in ppm.

Biotinyl-cadaverinyl-rubterolone (205)

exp: 168
DL394



A solution of HATU (13.0 mg, 34.0 µmol) in DMF (50 µL) was added to rubterolone D (**202**, 0.4 mg, 0.72 µmol) at r.t. To the deep green solution, DIPEA (6.0 µL, 35 µmol) and biotinyl cadaverine·TFA (4.0 mg, 8.3 µmol) were added and the mixture shaken at 35 °C for 7 h. The crude was diluted with H_2O (200 µL) and MeOH (200 µL) and then purified by RP-HPLC (Phenomonex C18(2) 250 x 10 mm; H_2O + 0.1 % formic acid/MeCN; 68/32 → 0/100; eluting at 50/50) to yield compound **205** as a deep red solid (0.1 mg, 16 %).

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{43}H_{54}O_{12}N_5S$ 864.3484, found 864.3468.

Table 4.6: ^{1}H-NMR (600 MHz) data for rubterolone **205**.

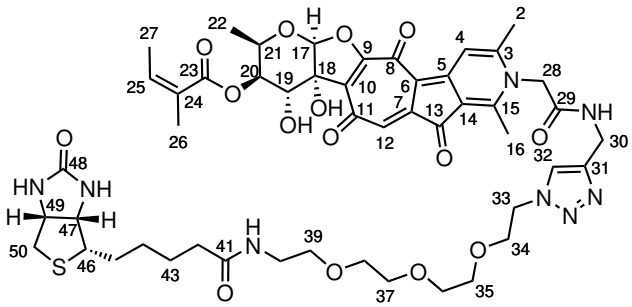
Pos.	δ_H[a]	mult. (J in Hz)	Pos.	δ_H[a]	mult. (J in Hz)
1			26	1.57	s
2	2.59	s	27	1.43	d (7.1)
3			28	5.02	br. s
4	8.41	s	29		
5			30	3.14	m
6			31	1.49	m
7			32	1.28	m
8			33	1.38	m
9			34	3.01	m
10			35		

Pos.	δ_H[a]	mult. (J in Hz)	Pos.	δ_H[a]	mult. (J in Hz)
11			36	2.04	t (7.3)
12	6.23	s	37	1.50	m
13			38	1.30	m
14			39a	1.45	m
15			39b	1.60	m
16	2.78	s	40	3.09	m
17	5.35	s	41	4.12	m
18			42		
19	5.08	d (4.0)	42a	4.30	m
20	4.70	dd (4.2; 1.3)	43	2.57	d (12.5)
21	4.25	q (6.4)	44	2.82	dd (12.4; 5.1)
22	0.98	d (6.6)	NH(1)	7.74	br. s
23			NH(2)	6.40	s
24			NH(3)	6.34	s
25	6.35	m			

[a] All values in ppm.

Biotin-PEG$_3$-rubterolone (206)

exp: 169
DL394



Biotin-PEG$_3$-azide conjugate (3.0 mg, 6.8 µmol) was added to a solution of propargyl rubterolone D (**203**, 0.6 mg, 1.0 µmol) in MeOH/(50/50, 400 µL). After vortexing the deep red mixture for 10 s, CuI (2.0 mg, 10.5 µmol) and TBTA (2.5 mg, 4.7 µmol) were added, the resulting mixture shortly vortexed and then shaken at 30 °C. The reaction was stopped after 2 h and the crude mixture was directly subjected to semi-preparative HPLC (H_2O/MeCN + 0.1 % formic acid 18/82 → 0/100, eluting at 40/60) to yield **206** as a deep red solid (0.5 mg, 48 %).

HRMS (ESI-TOF): calculated for $[M + H]^+$ $C_{49}H_{63}O_{15}N_8S$ 1035.4128, found 1035.4120.

Table 4.7: ^{1}H-NMR (600 MHz) and ^{13}C-NMR (150 MHz) data for rubterolone **206**.

Pos.	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)	Pos.	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)
1				31	143.6 s		
2	22.0 q	2.60	s	32	123.3 d	7.98	s

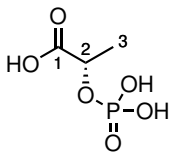
Pos.	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)	**Pos.**	δ_C mult.[a]	δ_H[a]	mult. (J in Hz)
3	157.9 s			33	50.0 t	3.37	t (4.2)
4	115.8 d	8.41	s	34	68.6 t	3.60	t (4.8)
5	n.a.			35 – 38c	69.5 t	3.51 – 3.56	m
6	109.9 s			39	68.9 t	3.39	t (5.3)
7	137.3 s			40	38.1 t	3.17	t (5.3)
8	n.a.			41	171.9 s		
9	163.8 s			42	34.8 t	2.06	t (7.3)
10	125.9 s			43	25.1 t	1.50	m
11	182.9 s			44	28.1 t	1.29	m
12	118.4 s	6.23	s	45	27.8 t	1.45	m
13	193.6 s					1.60	m
14	121.1 s			46	55.1 d	3.08	m
15	152.1 s			47	60.7 d	4.12	m
16	14.0 q	2.79	s	48	162.6 s		
17	102.8 d	5.35	s	49	59.0 d	4.30	t (6.4)
18	80.1 s			50	39.6 t	2.57	dd (12.4;2.3)
19	64.0 d	5.08	t (3.7)			2.81	m
20	71.6 d	4.70	d (4.1)	NH(1)		9.10	
21	64.3 d	4.24	q (6.2)	NH(2)		7.81	t (5.7)
22	24.9 q	0.98	d (6.2)	NH(3)		6.41	s
23	165.9 s			NH(4)		6.35	s
24	127.4 s			19-OH		5.80	br. s
25	137.1 d	6.34					
26	11.2 q	1.56	s				
27	13.4 q	1.43	d (6.3)				
28	51.5 d	5.06	s				
29	164.7 q						
30	34.7 t	4.41	d (5.4)				

[a] All values in ppm; [n.a.] not unambigously assigned.

4.8.3 Synthesis of 2-phospholactate

2-Phospholactate (208)

exp: 170
DL525/
DL526



To a solution of benzyl (*S*)-2-hydroxypropanoate (750 mg, 4.16 mmol) in pyridine (5.55 mL) was dropped diphenyl phosphoryl chloride (905 µL, 4.37 mmol) at 0 °C and the suspension was stirred at r.t. for 24 h. The reaction was stopped by addition of H_2O (1 mL) and the volatiles were removed *in vacuo*. The residue was dissolved in toluene (7 mL) and washed with H_2O, 1 M aq. HCl, sat. NaHCO3-solution and brine successively. The organic phase was dried over $MgSO_4$, filtered and the volatiles removed *in vacuo* to yield 1.54 g of a colorless oil, which was directly used in the next step.

The oil was dissolved in EtOH (41.7 mL) and PtO_2 (82.6 mg, 636 µmol) was added. Hydrogen gas from a balloon was bubbled through the stirred black suspension at r.t. for 3 h, then the mixture was left stirring under hydrogen atmosphere for additional 22 h with renewal of the atmosphere, when the balloon was depleted. After filtration of the mixture through a pad of Celite the volatiles were removed *in vacuo* to yield a greenish highly viscous oil. 2-PL was further purified via Chromabond C18 SPE cartridge (Macherey-Nagel). The flow-through (10 % MeOH in H_2O) was lyophilized and yielded 629 mg of **208** as colorless oil (47 % over two steps).

^{1}H-NMR (300 MHz**, D_2O):** δ = 4.71 (dq, J = 7.5, 6.9 Hz, 1 H, 2-H), 1.44 (t, J = 6.9 Hz, 3 H, 3-H) ppm.

^{13}C-NMR (75 MHz**, D_2O):** δ = 175.6 (d, C-1), 70.6 (dd, C-2), 18.8 (dq, C-3) ppm.

The analytical data is consistent with literature reports.[174]

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Selbstständigkeitserklärung

Ich erkläre, dass ich die vorliegende Arbeit selbständig und unter Verwendung der angegebenen Hilfsmittel, persönlichen Mitteilungen und Quellen angefertigt habe.

Hereby, I declare that I have composed the presented work independently on my own and without any other resources and personal communications than the ones indicated.

Ort, Datum Daniel Leichnitz