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Total synthesis of enantiopure lipids

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Chapter 2

Synthesis of hydroxyphthioceranic acid

In this chapter, a novel synthesis of hydroxyphthioceranic acid is presented. This approach allows to combine the synthesis of phthioceranic and hydroxyphthioceranic acid, reducing laborious purification considerably. Key to the success of this approach is a stereoselective allylic alkylation followed by a stereoselective dihydroxylation on the resulting terminal olefin. In addition, larger quantities of hydroxyphthioceranic acid can now be made available as the overall yield of the procedure has doubled compared to the previous report.

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2.1 Introduction

Deoxypropionates are a common motive in a variety of natural products. Many of these molecules have wide-spread, interesting functions. As a result, it is not without reason that the synthesis of deoxypropionates has received ample attention.^[1] Also our group has been involved in these investigations, and the stereoselective synthesis of a number of products has been reported using an iterative protocol employing copper catalysis.^[2]

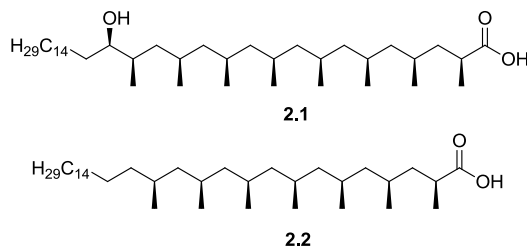


Figure 2.1 Structure of hydroxyphthioceranic (**2.1**) and phthioceranic acid (**2.2**)

Taking advantage of the acquired synthetic knowledge to prepare deoxypropionates, our group has devised a total synthesis of hydroxyphthioceranic acid over the past few years (Figure 2.1),^[3] initially in order to elucidate its absolute configuration. With the structure of **2.1** established, a more straightforward synthetic route could be envisioned without the need to invert the stereochemistry of the hydroxy group. In addition, the synthesis of **2.1** and **2.2** from a common intermediate is appealing, because both polypropionates are found in sulfolipid-1 (Figure 2.2, Chapter 4).^[4]

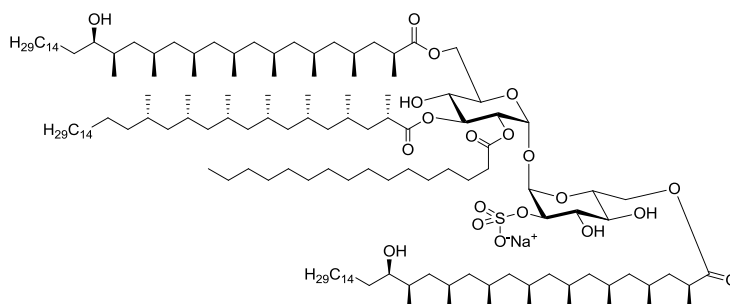


Figure 2.2 *sulfolipid-1*

Commencing the synthesis with the iterative deoxypropionate synthesis protocol, and subsequent functionalization towards **2.1** and **2.2** would streamline their syntheses

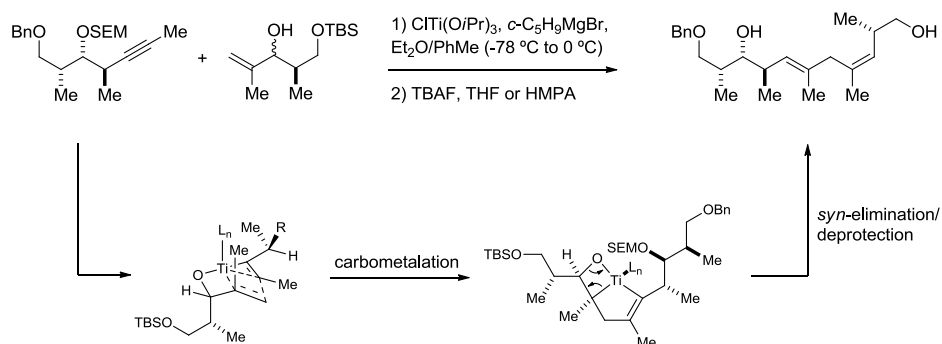
considerably. This chapter will focus on the combined synthesis of phthioceranic and hydroxyphthioceranic acid to ultimately use both in the synthesis of sulfolipid-1.

2.2 Novel stereoselective synthetic strategies towards 1,3-methyl arrays

Since the first reported synthesis of deoxypropionates by Oppolzer in 1986,^[5] many elegant catalytic and non-catalytic approaches towards the formation of stereoselective 1,3-methyl deoxypropionates have been reported. As these were only recently reviewed, an overview of the methods reported afterwards will be given.^[1, 6]

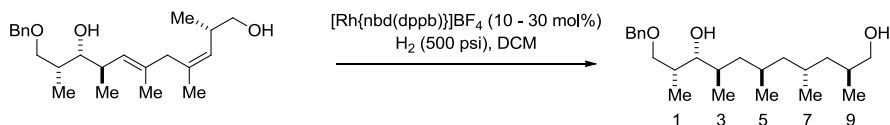
2.2.1 Metallacycle-mediated alkyne-allylic alcohol cross coupling and hydrogenation

The synthesis of deoxypropionates has mostly been carried out using iterative chain growth. Although this makes these syntheses modular with respect to the preparation of different stereoisomers without the need to start from the beginning, a convergent synthesis can greatly improve the step economy of well-defined targets. Recently, the group of Micalizio reported a convergent strategy towards deoxypropionates based upon an earlier reported stereoselective titanium-mediated reductive cross-coupling.^[7] After coupling the allylic alcohol and alkyne, a *syn*-elimination affords a (*Z,E*)-1,4-diene (Scheme 2.1). This step proceeds *via* a stereodefined oxatitanocyclobutane.



Scheme 2.1 Titanium mediated reductive cross-coupling

Subsequent hydroxy-directed hydrogenation of the alkene functions catalyzed by a rhodium catalyst affords the desired deoxypropionates with high stereoselectivity, although high hydrogen pressure (34 bar) and catalyst loading are needed (Scheme 2.2). The stereochemistry of the starting materials used in the cross-coupling determines the



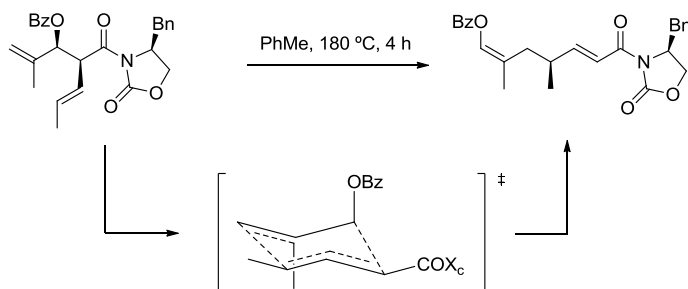
Scheme 2.2 Hydroxy-promoted, rhodium-catalyzed, stereoselective hydrogenation

stereochemical outcome of the product. By means of a small library of different stereodefined building blocks, a variety of products can thereby easily accessed.

The power of the methodology has been demonstrated with the synthesis of the C1 – C11 subunit of borrelidin and a very short synthesis of (–)-vittatalactone. However, the fact that this approach currently only allows the formation of the 3,5-*syn* and 7,9-*anti* configurations, limits its application in synthesis.

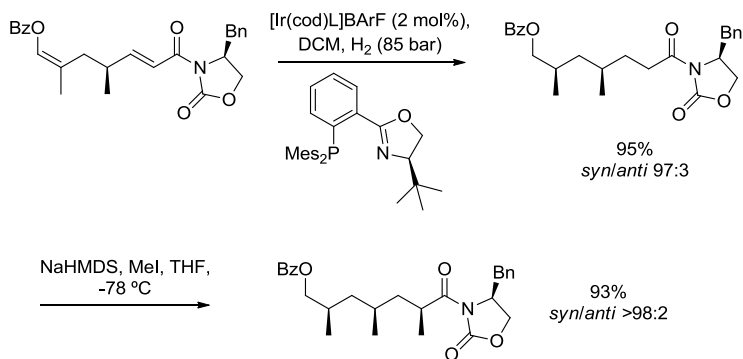
2.2.2 A non-iterative approach towards trideoxypropionates

In 2011, the group of Schneider reported the formation of deoxypropionates using a non-iterative three-step protocol.^[6] Starting from the product of an asymmetric aldol reaction using the Evans' chiral auxiliary, an oxy-Cope rearrangement delivers the α,β -unsaturated amide with excellent diastereoselectivity (>98:2, Scheme 2.3). The other diastereomer can be obtained using the *Z*-olefin.



Scheme 2.3 Oxy-Cope rearrangement towards deoxypropionates. X_c : Evans chiral auxiliary

Subsequent asymmetric hydrogenation using a chiral iridium catalyst based upon a PHOX-ligand gives rise to a second stereogenic center in high yield (Scheme 2.4). The hydrogenation is under perfect catalyst-control as both the *syn* and *anti* product can be formed in an excellent 97:3 diastereomeric ratio. Completion of the trideoxypropionate is achieved using the chiral-auxiliary-based stereoselective insertion of the last methyl ramification affording the trideoxypropionate in high yield in excellent diastereomeric ratios. A drawback of the chiral auxiliary approach is that the synthesis is not modular regarding



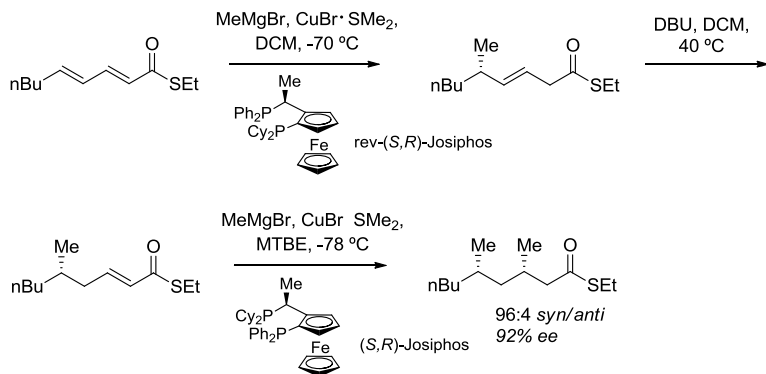
Scheme 2.4 Succeeding steps towards trideoxypropionates

the introduction of the last methyl group. Since the auxiliary controls the stereochemistry on the α -position, the epimer has to be prepared starting from the beginning.

Overall, the method allows the formation of all possible diastereomers in good yield and diastereoselectivity. Schneider *et al.* illustrate the usefulness of their approach with the synthesis of (+)-vittatalactone and (+)-norvittatalactone, two pheromones which have been isolated from the striped cucumber beetle *Acalymma vittatum*.^[9]

2.2.3 Combining asymmetric copper-catalyzed 1,6- and 1,4-conjugate additions

Feringa *et al.* reported in 2010 the combination of copper-catalyzed 1,6- and 1,4-conjugate additions to create deoxypropionates.^[2a] Using these strategies that involve the catalytic addition of Grignard reagents to α,β -unsaturated thioesters, a more direct approach to these architectures was identified. Starting from $\alpha,\beta,\gamma,\delta$ -unsaturated thioesters, readily prepared by an extended HWE reaction, an initial 1,6-conjugate addition with *rev*-Josiphos



Scheme 2.5 Combining 1,6- and 1,4-conjugate additions to create deoxypropionates

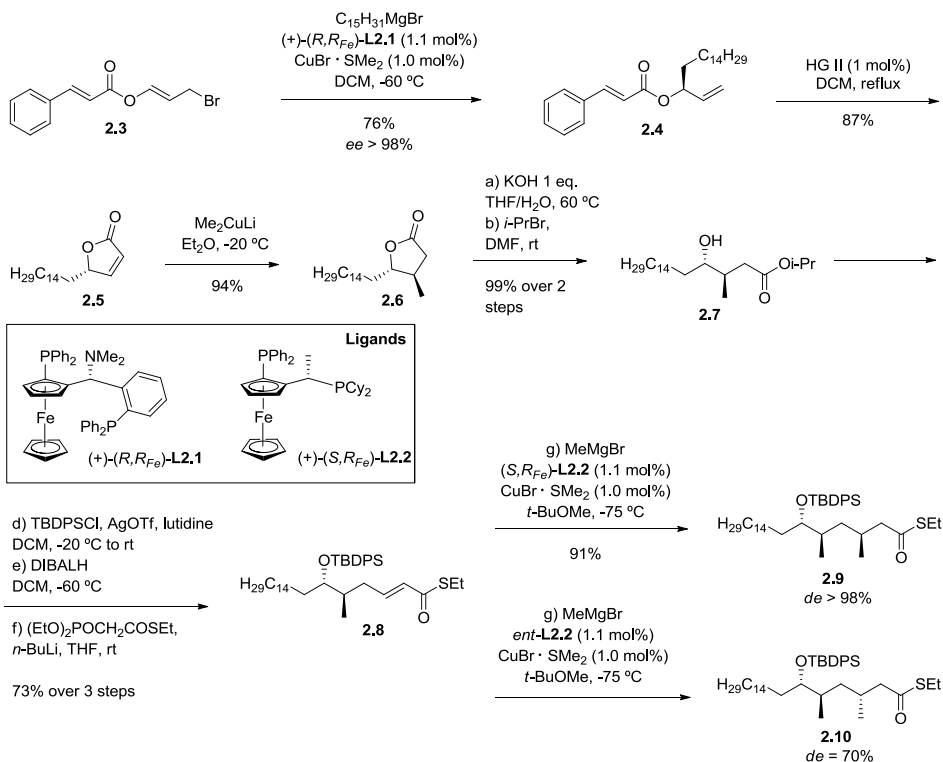
afforded an intermediate with one methyl group and a β,γ -unsaturated thioester in good yield and high *ee* (Scheme 2.5). Isomerization to acquire the α,β -unsaturated thioester needed for 1,4-addition, proved to be most effective using DBU. Although the isomerization was found to be an equilibrium (~90:10 in favor of the α,β -unsaturated thioester) and the products could not be separated, this did not hamper the succeeding 1,4-conjugate addition. The *syn* product was obtained in 63% yield, 96:4 *syn/anti* ratio and 92% *ee*, starting from the $\alpha,\beta,\gamma,\delta$ -unsaturated thioester. In addition, the *anti* product can be obtained although with slightly diminished selectivities.

In conclusion, the combined strategy allows the quick and high-yielding introduction of *syn*-oriented methyl substituents, albeit with somewhat lower *ee*'s than with the iterative 1,4-conjugate addition protocol.

2.3 Previous synthesis of hydroxyphthioceranic acid

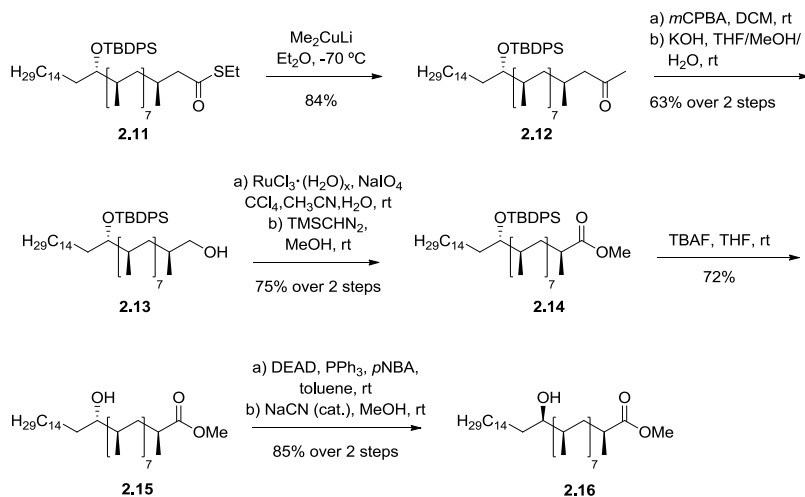
The initial approach towards **2.1**, as developed earlier in our group,^[3] was based on the copper-catalyzed asymmetric allylic alkylation of **2.3**, which, in turn, is prepared from cinnamoyl bromide and acrolein (Scheme 2.6).^[10] Addition of pentadecylmagnesium bromide, using $\text{CuBr}\cdot\text{SMe}_2$ and **L2.1**, provided **2.4** in 76% yield and 98% *ee*. As the stereochemistry of the hydroxyl group in natural **2.1** was unknown, a deliberate choice for the (*S*)-configuration was made, assuming that this could be adapted at a later stage via a Mitsunobu reaction should this be necessary. Ring-closing metathesis of **2.4** using 1 mol% of second-generation Hoveyda-Grubbs catalyst (HG II) afforded α,β -unsaturated lactone **2.5** in 87% yield. Using substrate control, 1,4-addition with the Gilman reagent Me_2CuLi gave *anti*-**2.6** as a single diastereomer in 94% yield.

At first, an attempt was made to reduce the lactone to the corresponding lactol, followed by Wittig or Horner-Wadsworth-Emmons (HWE) olefination to prepare compound **2.8**, after silylation. Although reduction of **2.6** with DIBALH afforded the lactol quantitatively, this compound resisted olefination. Initially, ring opening and esterification of the resulting acid were hampered by the strong tendency to cyclize again. Treatment with one equivalent of KOH in THF/water, followed by addition of an excess of *iso*-propyl bromide in DMF, however, allowed the isolation of ester **2.7** in near-quantitative yield.



Scheme 2.6 First approach to the synthesis of hydroxyphthioceranic acid

The secondary hydroxyl group of **2.7** was protected as its silyl ether, after which the ester moiety was reduced to the corresponding aldehyde with DIBALH. Subsequent HWE olefination afforded α,β -unsaturated thioester **2.8** in 73% yield over three steps. With **2.8** in hand, the question arose what the influence of the substrate would be on the diastereoselectivity of the copper-catalyzed 1,4-addition of MeMgBr using (+)-(*S,R*)- or (-)-(*R,S*)-Josiphos (**L2.2**) as the ligand. Analysis of both reactions by ¹H-NMR spectroscopy showed, in the case of (+)-(*S,R*)-Josiphos, a clear preference for the desired *syn*-product **2.9**, which was isolated in high yield and a *de* higher than 98%. The *anti*-product **2.10** was obtained with (-)-(*R,S*)-Josiphos in an acceptable but markedly lower *de* of 70%. The preparation of **2.9** set the stage for the introduction of all subsequent methyl substituents applying an iterative protocol following the sequence of DIBALH reduction/HWE olefination/asymmetric conjugate addition.^[2c, 11] Repetition of these steps led to **2.11** with eight methyl substituents in a 1,3-array as in natural **2.1** (Scheme 2.7).



Scheme 2.7 Synthesis of C17 *syn*- and *anti*-hydroxyphthioceranic acid methyl esters

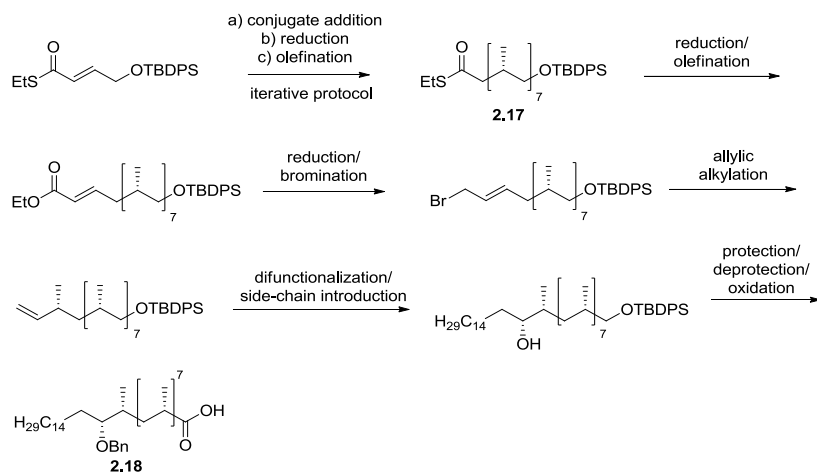
To install the carboxylic acid function of **2.1** at the correct position starting from **2.11**, one carbon had to be removed. To do so, the β -substituted thioester was converted into the corresponding methyl ketone using Me_2CuLi , affording **2.12** in 84% yield.^[12] This ketone was subsequently subjected to a regioselective Baeyer–Villiger oxidation employing *m*-chloroperbenzoic acid. As partial hydrolysis of the acetate took place in the Baeyer–Villiger oxidation, the crude mixture obtained was hydrolyzed to the primary alcohol **2.13** in 63% yield over two steps. Oxidation of the primary alcohol and deprotection of the secondary hydroxyl group would directly afford the target compound. However, it was realized that in order to compare the synthetic material with that of natural origin, it would be more convenient to have **2.1** available as its methyl ester. For this reason, alcohol **2.13** was oxidized using $\text{RuCl}_3 \cdot (\text{H}_2\text{O})_x$ and NaIO_4 and immediately treated with trimethylsilyl diazomethane to give methyl ester **2.14** in 75% yield over two steps. Deprotection with TBAF afforded the methyl ester of **2.1** (**2.15**) with the secondary alcohol at C17 in an *anti* configuration with respect to the methyl group at C16. To unambiguously assign the stereochemistry of C17 in natural **2.1**, **2.15** was also converted into its C17-OH epimer (**2.16**) by Mitsunobu reaction with *p*-nitrobenzoic acid. Trans-esterification with NaCN in MeOH finally afforded **2.16** in 85% yield over two steps. Overall, synthetic **2.1** was obtained in 1.4% yield over 32 steps starting from **2.3**.

The optical rotation of **2.15** and **2.16** turned out to be virtually identical ($[\alpha] = +16.0$ for

2.15 and $[\alpha] = +16.4$ for **2.16**, both in CHCl_3), and, in turn, close to that reported in the literature for a mixture of homologues ($[\alpha] = +23$).^[13] An extract of cell-wall lipids containing sulfolipid-1 (Chapter 4), prepared following the procedure of Goren, was trans-esterified with NaCN in MeOH to give a complex mixture of polypropionate methyl esters.^[4a] The presence of **2.15** or **2.16** in the natural sample was proven by mass spectrometry. Analysis with HPLC-ELSD revealed a significant difference in retention time between **2.15** and **2.16** and comparison with the natural sample confirmed that *anti*-**2.15** was not present in the natural sample, whereas *syn*-**2.16** was. The esterified natural sample was compared to synthetic **2.15** and **2.16** by $^1\text{H-NMR}$ spectroscopy. Although the natural sample consists of a mixture of homologues, the chemical shift for the methine-proton next to the OH-group was not obscured. Inspection of the $^1\text{H-NMR}$ spectrum of synthetic *anti*-**2.15** and *syn*-**2.16** revealed a small but distinct difference (3.47 and 3.50 ppm, respectively). A perfect match with *syn*-**2.16** was found for the natural sample which provided strong evidence for a *syn* relationship in the natural product. Additional and conclusive evidence was obtained by comparing the $^{13}\text{C-NMR}$ spectra of all samples. Both **2.15** and **2.16** displayed distinct differences in chemical shift for the carbon atoms in the proximity of the secondary hydroxyl group. The natural product was shown to be identical with *syn*-**2.16**, whereas *anti*-**2.15** was not detected. These combined data established that **2.1** and its methyl ester **2.16** have the same stereochemistry as natural hydroxyphthioceranic acid.

2.4 Strategy for the combined synthesis of HPA and PA

In Scheme 2.8, the most advanced common intermediate for a synthesis of both **2.1** and **2.2** is **2.17**,^[11] with seven methyl branches installed.^[2b] In order to obtain **2.1**, we planned to introduce the eighth methyl branch via copper-catalyzed allylic substitution.^[14] Unlike conjugate addition, allylic substitution enables subsequent difunctionalization of the resulting alkene in order to introduce the hydroxyl group and to append the required alkyl chain to the terminus. Even though the asymmetric allylic alkylation is a reasonably well explored reaction, we were not certain of its viability in the presence of such an extended array of chiral centers nearby. Moreover, enantio- or diastereoselective difunctionalization of monosubstituted aliphatic terminal olefins is notoriously difficult and only few successful examples have been reported in the literature.^[15] Finally, as **2.18** will have to be esterified



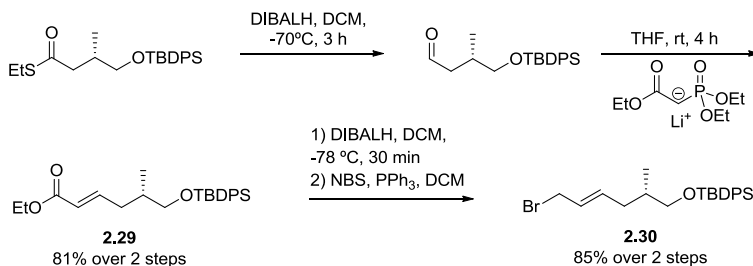
Scheme 2.8 Proposed synthetic pathway for the synthesis of hydroxyphthioceranic acid

to the trehalose core, its hydroxyl function needed protection in such a way that deprotection would not be detrimental to the rest of the molecule.

2.5 Synthesis

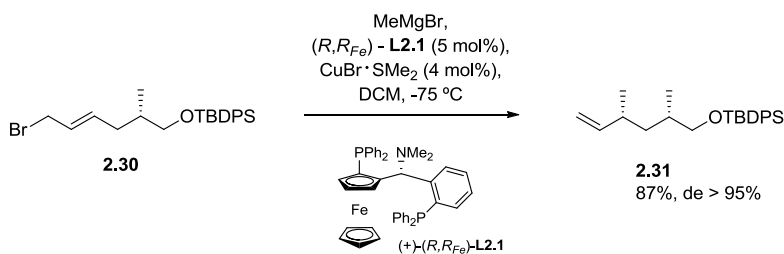
Starting from α,β -unsaturated thioester **2.19**, polyketide **2.17** was obtained in good yield with seven methyl substituents following our iterative 1,4-addition procedure (Scheme 2.9).^[11] As we planned to prepare sulfolipid-1 in a later stage, we first decided to prepare phthioceranic acid, one of its components. To do so, the aliphatic tail was introduced by reduction of the thioester, transformation of the alcohol formed into a leaving group and substitution using the desired Grignard reagent. Subsequently, the silyl ether was removed and the resulting primary alcohol was oxidized to afford **2.2** in yields corresponding to those reported.

Towards the synthesis of benzylether-protected **2.18**, intermediate **2.17** was reduced with DIBALH and the aldehyde was submitted to a HWE olefination, affording oxo-ester **2.20** in 85% yield over two steps. Reduction of **2.20** with DIBALH furnished allylic alcohol **2.21**, which was, in turn, converted to allylic bromide **2.22**, using NBS/ PPh_3 in 88% yield. In order to study the subsequent functionalizations we prepared the less costly model substrate **2.30** using the same approach as for **2.22** (Scheme 2.10).



Scheme 2.10 Preparation of a model substrate for the asymmetric allylic alkylation

We were pleased to see that the planned copper-catalyzed asymmetric allylic alkylation of **2.30** with (R,R) -**L2.1** and MeMgBr afforded terminal olefin **2.31** in 87% yield (Scheme 2.11). Preparation of the corresponding *anti* product (**2.32**, not shown) with *ent*-**L2.1** confirmed that both *syn* and *anti* products can be obtained in a *de* >95%, meaning that the reaction is under perfect catalyst control.



Scheme 2.11 Cu-catalyzed asymmetric allylic alkylation on a model substrate

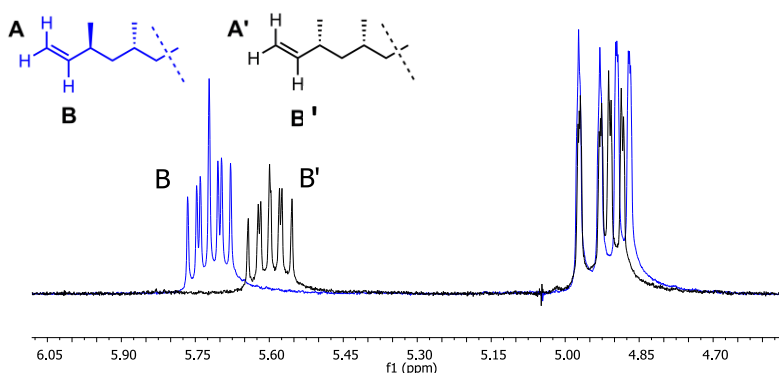
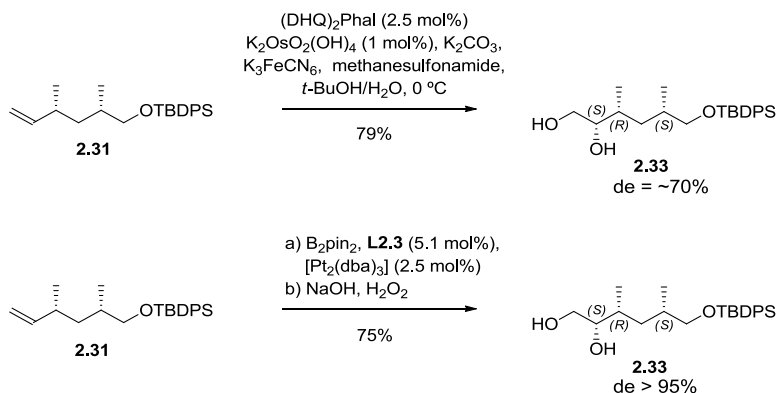


Figure 2.3 Highly diastereoselective allylic alkylation affording *syn* and *anti* products

Figure 2.3 shows that the olefinic protons 'B' display a small but distinct difference in chemical shift in the ^1H -NMR spectrum. Comparison of both products with related

compounds reported earlier, demonstrated the correct assignment of the relative and absolute configurations.^[16]

With terminal olefin **2.31** in hand, the Sharpless dihydroxylation reaction was explored for the subsequent difunctionalization (Scheme 2.12).^[17] Although the yield of the dihydroxylation was satisfactory, the 5:1 *syn* : *anti* ratio obtained on model substrate **2.33** having two methyl substituents was somewhat disappointing (Figure 2.4).



Scheme 2.12 Dihydroxylation of terminal olefins using procedures by Sharpless and Morken

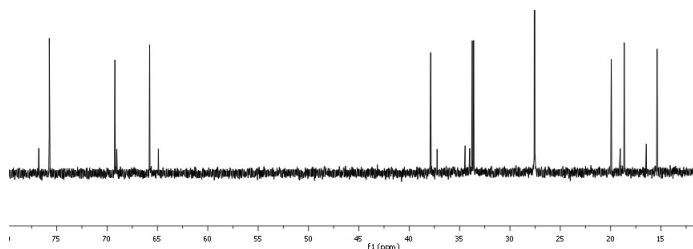


Figure 2.4 Part of the ¹³C NMR spectrum of **2.33**, prepared using the Sharpless dihydroxylation reaction, and indicating the formation of the *syn* (major) and *anti* (minor) diol

In 2009, an intriguing enantioselective diboration reaction was reported, employing bis(pinacolato)diboron (B₂pin₂) and a combination of [Pt₂(dba)₃] and phosphonite **L2.3** as the catalyst.^[18] Oxidation of the diboronate with H₂O₂ afforded diols in high enantioselectivities. As the reaction was reported to be applicable to unfunctionalized aliphatic terminal olefins, this alternative approach was employed. When we subjected model substrate **2.31** (Scheme 2.12) to the conditions described in the study of Morken *et al.* we observed the *syn* product with complete selectivity by ¹³C-NMR spectroscopy

(Figure 2.5). As the yield was comparable to that obtained in the Sharpless dihydroxylation reaction, we decided to use the Morken dihydroxylation procedure in our synthesis.

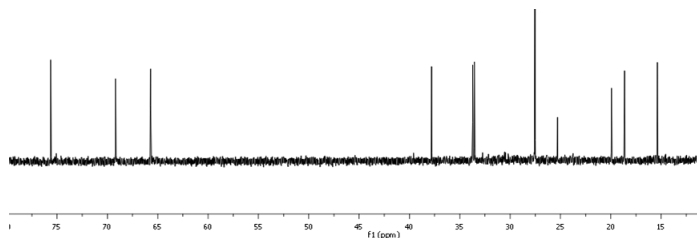
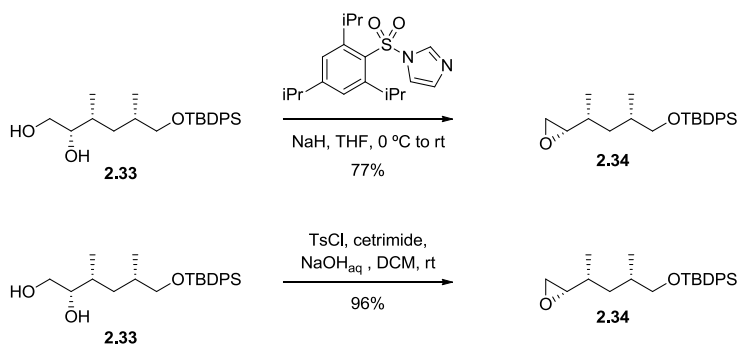


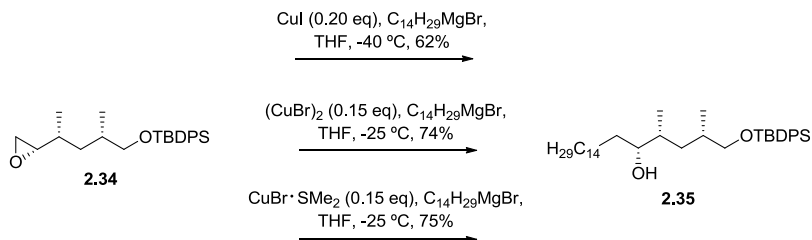
Figure 2.5 Part of the ^{13}C -NMR spectrum of **2.33**, prepared using the Morken dihydroxylation reaction.

We then envisioned that the diol could be transformed into the epoxide, followed by a ring-opening of the epoxide. Formation of **2.34** was initially accomplished using the sterically hindered *N*-trisylimidazole in the presence of sodium hydride (Scheme 2.13). However, during the course of our studies we found that this expensive reagent could be replaced with low-cost TsCl under phase-transfer conditions, in addition leading to improved yields.^[19]



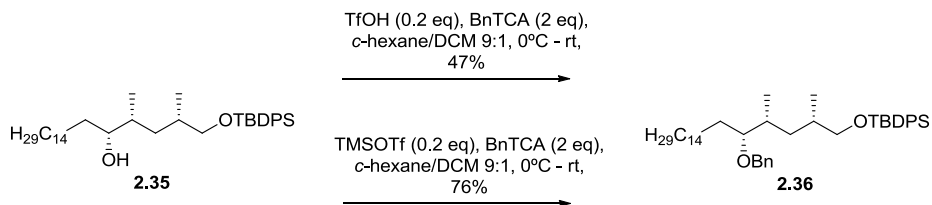
Scheme 2.13 Formation of the epoxide (cetrimide = hexadecyltrimethylammonium bromide)

Ring opening of the epoxide was studied with Grignard reagents and different copper salts. The use of $(\text{CuBr})_2$ and $\text{CuBr}\cdot\text{SMe}_2$ proved to be most effective, affording **2.35** in 74% and 75% yield, respectively. This influence of the counterion had been observed before (Scheme 2.14).^[20]



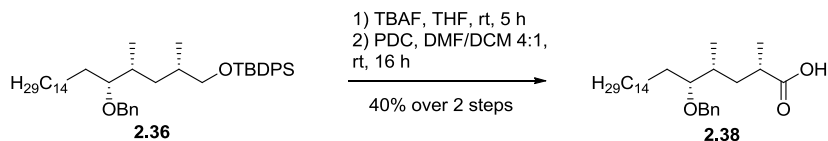
Scheme 2.14 Epoxide ring opening using Grignard reagents and Cu(I) salts

To protect the secondary alcohol of **2.35**, a range of basic conditions were explored. Unfortunately, all of these indicated, at best, only minimal amounts of conversion (<5%). We then switched to (Lewis) acidic conditions using benzyl 2,2,2-trichloroacetimidate. The combination with triflic acid afforded benzyl ether **2.36**, although in a somewhat disappointing 47% yield (Scheme 2.15). However, TMSOTf gave **2.36** in a more satisfying 76% yield.^[21] It was observed that the amount of DCM has to be kept to a minimum, as an increase leads to the formation of multiple side-products.



Scheme 2.15 Protection of the secondary alcohol

The subsequent deprotection of the silyl ether with TBAF to the primary alcohol (**2.37**, structure not shown) and oxidation using PDC were facile, affording the carboxylic acid **2.38** in acceptable yield (Scheme 2.16).



Scheme 2.16 Final steps using the model substrate

To prepare our actual target molecule, we carried on with the asymmetric allylic alkylation. To obtain the same yields as with our model substrate we needed a slight increase of the catalyst loading (from 5 to 7 mol%). The terminal olefin **2.23** was obtained

in 88% yield and a >95:5 diastereoselectivity in favour of the *syn* product (Scheme 2.9).

When the optimal conditions for the dihydroxylation were applied to substrate **2.23** with eight methyl groups, only 5–10% of the desired product was obtained. After considerable experimentation, we discovered that with a twofold increase of the catalyst concentration and three equivalents of B₂pin₂, diol **2.24** was obtained in a gratifying 98% yield and >95% *de*. It represents the first application of this methodology to the synthesis of a natural product. Conversion of **2.24** under the aforementioned phase-transfer conditions afforded epoxide **2.25** in 88% yield, which was opened with tetradecylmagnesium bromide, employing copper catalysis. Analysis of alcohol **2.26** by ¹³C-NMR spectroscopy provided convincing evidence for the formation of the *syn* alcohol (Figure 2.6). Its chemical shifts match those of *syn*-**2.16** reported by Minnaard and ter Horst.^[3]

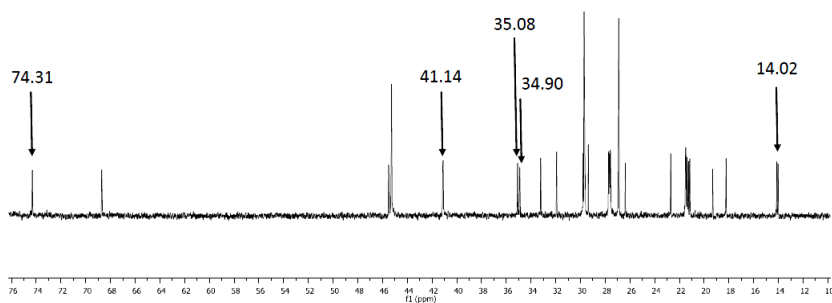


Figure 2.6 Part of the ¹³C-NMR spectrum of **2.25** indicating formation of the *syn* alcohol

TMSOTf-catalyzed protection of the secondary alcohol with benzyl 2,2,2-trichloroacetimidate, afforded benzyl ether **2.27** in 76% yield. The silyl ether of **2.27** was cleaved with TBAF to afford primary alcohol **2.28** in high yield. As we were not completely satisfied with the yield of the PDC oxidation on our model substrate, we studied an alternative approach for the formation of the carboxylic acid. Oxidation with TEMPO, NaOCl and NaClO₂ finally gave **2.18** in an excellent yield of 90%.^[22] Overall, **2.18** was obtained in a very satisfying 3.0% yield over 32 steps.

2.6 Conclusions

To embark on the synthesis of Ac₂SGL and sulfolipid-1 (Chapter 3 and 4), access to substantial quantities of phthioceranic and hydroxyphthioceranic acid was needed. In this chapter we demonstrate that it is now possible to combine the syntheses of both fatty acids

and diverge at a late stage. This reduces the number of laborious purifications. To functionalize towards hydroxyphthioceranic acid, the most crucial steps were an asymmetric allylic alkylation and an asymmetric diboration/dihydroxylation. Both steps showed to be highly stereoselective and afforded the corresponding products in high yield as shown by NMR. Next to a model substrate, benzyloxyphthioceranic acid was prepared in 32 steps, a number similar to that of the earlier reported synthesis by ter Horst. However, the overall yield was doubled to 3.0%. The higher yield resulted in the larger quantities necessary for the preparation of both sulfoglycolipids.

2.7 Experimental section

General remarks

All reactions were performed using oven or flame-dried glassware and dry solvents. Solvents were distilled prior to use: MTBE, Et₂O and THF (Na/benzophenone), DCM (CaH₂) or taken from a MBraun solvent purification system (SPS-800). All other reagents were purchased from Sigma Aldrich, Acros, TCI Europe, Alfa Aesar, Chempur or Fluorochem, and used without further purification unless noted otherwise. Grignard reagents were titrated using *s*-BuOH and catalytic amounts of 1,10-phenanthroline. Ligand **L2.3** and [Pt₂(dba)₃] were prepared following a literature procedure and stored in a glovebox afterwards.^[18a] B₂pin₂ was recrystallized from pentane prior to use.

¹H- and ¹³C-NMR spectra were recorded on a Varian AMX400 or a Varian 400-MR (400, 100.59 MHz, respectively). Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl₃: δ 7.26 for ¹H, δ 77.0 for ¹³C, CD₃OD: δ 3.31 for ¹H, C₆D₆: δ 128.06 for ¹³C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants *J* (Hz), and integration. Due to the (multiple) long alkyl chains in some of the compounds we unfortunately were not able to resolve all the individual signals for every carbon atom in the spectra. High resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL or on a AEI-MS-902 spectrometer.

Flash chromatography was performed using SiliCycle silica gel type SiliaFlash P60 (230 – 400 mesh) as obtained from Screening Devices or with automated column chromatography using a Reveleris flash system purchased from Grace Davison Discovery Sciences.

Columns for automated chromatography were obtained from Grace Davison or Screening Devices. TLC analysis was performed on Merck silica gel 60/Kieselguhr F254, 0.25 mm. Compounds were visualized using either Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL)) or a KMnO₄ stain (K₂CO₃ (40 g), KMnO₄ (6 g), H₂O (600 mL) and 10% NaOH (5 mL)).

Copper-catalyzed conjugate addition to α,β -unsaturated thioesters using MeMgBr, representative procedure A.

Josiphos-CuBr (**L2.2**) (1 mol%) was dissolved in *t*-BuOMe and stirred at rt for 30 min under nitrogen atmosphere in a flame-dried Schlenk. The mixture was cooled to -75 °C and MeMgBr (1.2 eq, 3 M solution in Et₂O) was added dropwise. After stirring for 10 min, a solution of thioester in *t*-BuOMe (final substrate concentration is 0.13 M) was added via a syringe pump over 1 – 2 h. The reaction mixture was stirred at -75 °C for 16 h, quenched by the addition of MeOH and allowed to warm to rt. A saturated aqueous NH₄Cl solution was added, the phases were separated and the aqueous layer was extracted with Et₂O. The combined organic phases were dried over MgSO₄, filtered, concentrated under reduced pressure and the product was purified by flash chromatography (pentane/Et₂O 40:1).

Thioester reduction using DIBAL-H, representative procedure B.

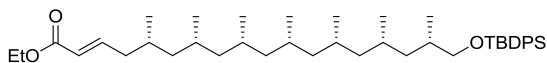
To a solution of the thioester in DCM (0.2 M) at -65 °C under nitrogen was added DIBAL-H (1.2 eq, 1 M solution in DCM). The mixture was stirred until TLC showed complete consumption of the starting material after which the reaction was quenched with an aliquot of a saturated solution of Rochelle's salt (potassium sodium tartrate) and the mixture was stirred for 1 h at rt. The phases were separated, and the aqueous layer extracted with Et₂O (3x). The combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (pentane/Et₂O 40:1) to give the pure aldehyde.

Horner-Wadsworth-Emmons olefination, representative procedure C.

To a stirred solution of (EtO)₂POCHCOSEt (1.6 eq) in THF at 0 °C under nitrogen was added *n*-BuLi (1.3 eq, 1.6 M solution in hexane). The reaction mixture was stirred for an additional 20 min. A solution of the corresponding aldehyde in THF (final substrate concentration is 0.15 M) was added dropwise, and after addition the reaction mixture was slowly warmed to rt and subsequently stirred until TLC showed complete disappearance of the aldehyde (3-4 h). The reaction mixture was quenched with a saturated aqueous NH₄Cl solution. The phases were separated and the aqueous layer extracted with 3 portions of

Et₂O. The combined organic phases were dried over MgSO₄, concentrated under reduced pressure, and the product purified by flash chromatography (pentane/Et₂O 50:1) to afford the desired α,β -unsaturated thioester.

(5*R*,7*R*,9*R*,11*S*,13*S*,15*S*,17*S*,E)-ethyl 18-((tert-butyl)diphenylsilyloxy)-5,7,9,11,13,15,17-heptamethyloctadec-2-enoate (2.20):

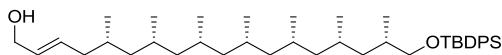


A flame dried Schlenk equipped with

stirring bar was charged with THF (4.5 mL, final concentration of substrate is 0.15 M) and triethyl phosphonoacetate (1.6 eq, 242 mg, 214 μ L, 1.08 mmol). The solution was cooled to 0 °C and *n*-BuLi (506 μ L, 0.81 mmol, 1.6 M solution in hexanes) was added dropwise over a period of 10 min. After an additional 20 min of stirring, the aldehyde obtained from the reduction of **2.17** with DIBALH, was added as a solution in THF (1 mL). The reaction was allowed to warm up to rt and TLC showed complete consumption of starting material after 14 h. The reaction was quenched with a saturated solution of aqueous NH₄Cl (5 mL) and the layers were separated. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were dried over anhydrous MgSO₄, filtered, concentrated and purified using column chromatography (pentane/Et₂O 50:1) to afford pure α,β -unsaturated ester **2.20** (381 mg, 85%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.69 (dd, *J* = 7.8, 1.5, 4H), 7.47 – 7.33 (m, 6H), 6.96 (ddd, *J* = 15.3, 8.0, 7.0, 1H), 5.83 (dt, *J* = 15.5, 1.3, 1H), 4.20 (q, *J* = 7.1, 2H), 3.53 (dd, *J* = 9.8, 4.9, 1H), 3.43 (dd, 9.8, 6.4, 1H), 2.33 – 2.17 (m, 1H), 2.0 – 1.93 (m, 1H), 1.83 – 1.67 (m, 2H), 1.67 – 1.48 (m, 6H), 1.47 – 1.35 (m, 2H), 1.33 – 1.26 (m, 6H), 1.25 – 1.15 (m, 6H), 1.07 (s, 9H), 0.95 (d, *J* = 6.7, 3H), 0.93 – 0.76 (m, 18H); **¹³C NMR** (101 MHz, CDCl₃) δ 166.58, 148.21, 135.60, 134.04, 129.43, 127.52, 122.43, 68.64, 60.09, 45.45, 45.25, 45.22, 44.36, 41.06, 39.03, 35.41, 33.18, 31.88, 29.86, 27.67, 27.49, 27.45, 26.88, 22.69, 21.40, 21.33, 21.29, 21.12, 20.91, 20.52, 19.30, 18.22, 14.28; **HRMS**-(APCI+) calculated for C₃₃H₅₉O₂Si [M - C₆H₅]⁺ 585.4703 Da, found 585.4697 Da.

5*R*,7*R*,9*R*,11*S*,13*S*,15*S*,17*S*,E)-18-((tert-butyl)diphenylsilyloxy)-5,7,9,11,13,15,17-

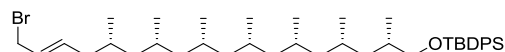


heptamethyloctadec-2-en-1-ol (2.21): To a stirred solution of **2.20** (333 mg, 0.50 mmol) in DCM (2.5 mL, 0.2 M) at –75°C was added DIBAL-H (3 eq, 1.5 mL, 1.50 mmol, 1 M solution in DCM). The reaction was allowed to stir for 30 minutes after which TLC showed that no starting material was left. The mixture was quenched with a saturated aqueous Rochelle salt solution (5 mL) and allowed to warm up over 2 h with vigorous stirring. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The

combined organic layers were dried over MgSO_4 and all volatiles were evaporated. The product was purified using column chromatography (pentane/ Et_2O 5:1) to afford allylic alcohol **2.21** (301 mg, 97%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.71 (dd, $J = 7.7, 1.5$, 4H), 7.50 – 7.34 (m, 6H), 5.73 – 5.64 (m, 2H), 4.12 (d, $J = 4.6$, 2H), 3.56 (dd, $J = 9.8, 4.9$, 1H), 3.45 (dd, $J = 9.8, 6.4$, 1H), 2.17 – 2.11 (m, 1H), 1.88 – 1.75 (m, 2H), 1.70 – 1.53 (m, 7H), 1.46 – 1.38 (m, 1H), 1.32 – 1.18 (m, 7H), 1.08 (s, 9H), 0.98 (d, $J = 6.7$, 3H), 0.92 – 0.84 (m, 21H); **^{13}C NMR** (101 MHz, CDCl_3) δ 135.58, 134.03, 131.75, 130.23, 129.42, 127.52, 68.64, 63.77, 45.49, 45.36, 45.30, 45.27, 44.32, 41.06, 38.98, 33.17, 30.17, 27.67, 27.52, 27.49, 27.48, 27.46, 26.89, 21.42, 21.33, 21.13, 21.04, 20.42, 19.29, 18.22; **HRMS**-(APCI+) calculated for $\text{C}_{41}\text{H}_{68}\text{O}_2\text{SiNa}$ [$\text{M} + \text{Na}$]⁺ 643.4881 Da, found 643.4886 Da.

(((2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,*E*)-18-bromo-2,4,6,8,10,12,14-heptamethyloctadec-16-en-1-yl)oxy)(tert-butyl)diphenylsilane (2.22):

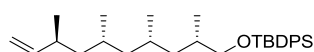


To allylic alcohol **2.21** (272 mg,

0.44 mmol) in DCM (2.2 mL, 0.2 M) was added PPh_3 (1.2 eq, 138 mg, 0.53 mmol). After all PPh_3 had dissolved, the solution was cooled to 0°C and NBS (1.3 eq, 101 mg, 0.57 mmol) was added in one portion. The reaction was stirred for 1 h at 0°C and an additional hour at rt after which the reaction was quenched with pentane (20 mL). The white precipitate was removed by filtration over Celite. The cake was rinsed with pentane (20 mL) and the collected solution was evaporated to dryness. The crude product was purified using column chromatography (pentane/ Et_2O 200:1) to afford allylic bromide **2.22** (265 mg, 88%) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.71 (dd, $J = 7.7, 1.6$, 4H), 7.50 – 7.34 (m, 6H), 5.85 – 5.63 (m, 2H), 3.98 (d, $J = 6.8$, 2H), 3.56 (dd, $J = 9.8, 5.0$, 1H), 3.46 (dd, $J = 9.8, 6.4$, 1H), 2.18 – 2.12 (m, 1H), 1.91 – 1.81 (m, 1H), 1.78 (dd, $J = 12.4, 6.4$, 1H), 1.71 – 1.54 (m, 7H), 1.48 – 1.38 (m, 1H), 1.29 – 1.18 (m, 7H), 1.09 (s, 9H), 0.98 (d, $J = 6.7$, 3H), 0.94 – 0.79 (m, 21H); **^{13}C NMR** (101 MHz, CDCl_3) δ 135.61, 135.15, 134.05, 129.44, 127.60, 127.54, 68.69, 45.54, 45.42, 45.35, 45.33, 44.33, 41.12, 38.81, 33.42, 33.22, 30.21, 27.73, 27.58, 27.56, 27.53, 26.92, 21.45, 21.37, 21.17, 21.02, 20.44, 19.32, 18.24; **HRMS**-(ESI+) calculated for $\text{C}_{41}\text{H}_{68}\text{OSi}^{79}\text{Br}$ [$\text{M} + \text{H}$]⁺ 683.4223 Da, found 683.4217 Da.

tert-butylidiphenyl(((2*S*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethyldec-9-en-1-yl)oxy)silane: The anti-

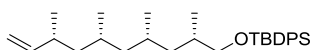


product shown in the ^1H -NMR trace (Figure 2.3) was prepared analogous to compound **2.32** but using 2 mol% of

copper catalyst based on **ent-L2.1**. Although incomplete conversion was obtained, the product was obtained as a colorless oil in 52% yield (*de* > 95% according to ^1H NMR) after purification by column chromatography (silica, pentane).

^1H NMR (400 MHz, CDCl_3) δ 7.75 – 7.56 (m, 4H), 7.50 – 7.31 (m, 6H), 5.72 (ddd, J = 17.4, 10.3, 7.3, 1H), 4.98 – 4.87 (m, 2H), 3.52 (dd, J = 9.8, 5.0, 1H), 3.42 (dd, J = 9.7, 6.5, 1H), 2.29 – 2.14 (m, 1H), 1.77 – 1.67 (m, 1H), 1.62 – 1.47 (m, 2H), 1.42 – 1.32 (m, 2H), 1.32 – 1.13 (m, 4H), 1.06 (s, 9H), 0.95 (d, J = 3.5, 3H), 0.94 (d, J = 3.5, 2H), 0.83 (d, J = 4.8, 3H), 0.81 (d, J = 4.7, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 145.63, 135.64, 135.61, 134.08, 129.45, 127.54, 111.73, 68.72, 45.69, 43.97, 41.29, 35.03, 33.16, 27.57, 27.52, 26.89, 20.88, 20.67, 19.55, 19.31, 18.14; HRMS-(ESI+) calculated for $\text{C}_{30}\text{H}_{46}\text{OSiNa}$ [$\text{M} + \text{Na}$] $^+$ 473.3216 Da, found 473.3207 Da.

tert-butylidiphenyl(((2S,4S,6R,8R)-2,4,6,8-tetramethyldec-9-en-1-yl)oxy)silane: The *syn*

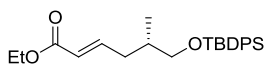


product shown in the ^1H -NMR trace (Figure 2.3) was prepared analogous to compound **2.31** but using 3 mol% of

the copper catalyst based on **L2.1**. The product was obtained as a colorless oil in 82% yield (*de* > 95% as judged by ^1H -NMR) after purification by column chromatography (pentane).

^1H NMR (400 MHz, CDCl_3) δ 7.75 – 7.56 (m, 4H), 7.51 – 7.31 (m, 6H), 5.60 (ddd, J = 17.2, 10.2, 8.2, 1H), 4.99 – 4.86 (m, 2H), 3.51 (dd, J = 9.7, 5.1, 1H), 3.41 (dd, J = 9.8, 6.4, 1H), 2.26 – 2.15 (m, 1H), 1.78 – 1.66 (m, 1H), 1.61 – 1.44 (m, 2H), 1.41 – 1.20 (m, 6H), 1.06 (s, 9H), 0.97 (d, J = 6.7, 3H), 0.93 (d, J = 6.7, 3H), 0.81 (d, J = 6.5, 3H), 0.79 (d, J = 6.5, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 144.66, 135.64, 135.63, 129.46, 127.55, 112.59, 68.80, 45.86, 43.86, 41.50, 35.62, 35.62, 33.13, 27.54, 27.43, 26.91, 21.63, 20.66, 20.47, 19.32, 18.07; HRMS-(ESI+) calculated for $\text{C}_{30}\text{H}_{46}\text{OSiNa}$ [$\text{M} + \text{Na}$] $^+$ 473.3216 Da, found 473.3210 Da.

(S,E)-ethyl 6-((tert-butylidiphenylsilyl)oxy)-5-methylhex-2-enoate (2.29): The title compound

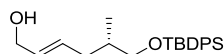


was prepared following the same procedure as used for compound **2.20**. The product was obtained as a colorless oil (81%).

^1H NMR (400 MHz, CDCl_3) δ 7.66 (dd, J = 7.2, 0.7, 4H), 7.48 – 7.34 (m, 6H), 7.01 – 6.87 (m, 1H), 5.84 (d, J = 15.6, 1H), 4.20 (q, J = 7.1, 2H), 3.52 (dd, J = 9.8, 5.0, 1H), 3.42 (dd, J = 9.8, 6.4, 1H), 2.53 – 2.39 (m, 1H), 2.15 – 1.98 (m, 1H), 1.87 (m, 1H), 1.30 (t, J = 7.1, 3H), 1.07 (s, 9H), 0.92 (d, J = 6.8, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 166.54, 147.90, 135.56,

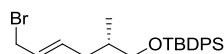
135.54, 133.70, 133.68, 129.57, 127.61, 122.52, 68.11, 60.10, 36.04, 35.36, 26.83, 19.27, 16.42, 14.28; **HRMS**-(APCI+) calculated for $C_{19}H_{29}O_3Si$ [$M - C_6H_5$]⁺ 333.1886 Da, found 333.1881 Da.

(S,E)-6-((tert-butyl)diphenylsilyloxy)-5-methylhex-2-en-1-ol: The title compound was prepared following the same procedure as used for compound **2.21**. The product was obtained as a colorless oil (87%).



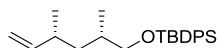
¹H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, $J = 7.7, 1.6$, 4H), 7.49 – 7.33 (m, 6H), 5.71 – 5.55 (m, 2H), 4.06 (s, 2H), 3.52 (d, $J = 5.9$, 2H), 2.35 – 2.16 (m, 1H), 2.02 – 1.85 (m, 1H), 1.85 – 1.70 (m, 1H), 1.09 (s, 9H), 0.94 (d, $J = 6.7$, 3H); **¹³C NMR** (101 MHz, $CDCl_3$) δ 135.60, 135.59, 133.92, 133.91, 131.49, 130.34, 129.51, 127.55, 68.14, 63.75, 35.87, 35.81, 26.85, 19.29, 16.52; **HRMS**-(APCI+) calculated for $C_{23}H_{32}O_2SiNa$ [$M + Na$]⁺ 391.2064 Da, found 391.2064 Da.

(S,E)-((6-bromo-2-methylhex-4-en-1-yl)oxy)(tert-butyl)diphenylsilane (2.30): The title compound was prepared following the same procedure as used for compound **2.22**. The product was obtained as a colorless oil (97%).



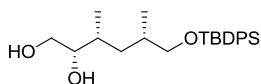
¹H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 4H), 7.48 – 7.33 (m, 6H), 5.78 – 5.62 (m, 2H), 3.93 (d, $J = 6.2$, 2H), 3.50 (dd, $J = 5.9, 1.9$, 2H), 2.33 – 2.23 (m, 1H), 2.00 – 1.89 (m, 1H), 1.83 – 1.70 (m, 1H), 1.08 (s, 9H), 0.93 – 0.91 (d, $J = 6.7$, 3H); **¹³C NMR** (101 MHz, $CDCl_3$) δ 135.60, 135.59, 134.87, 133.88, 133.86, 129.54, 127.69, 127.59, 68.08, 35.74, 35.73, 33.40, 26.88, 19.31, 16.45; **HRMS**-(APCI+) for $C_{23}H_{32}OSiBr$ [$M + H$]⁺ calculated 431.1406 Da, found 431.1400 Da.

tert-butyl(((2S,4R)-2,4-dimethylhex-5-en-1-yl)oxy)diphenylsilane (2.31): The title compound was prepared following the same procedure as used for compound **2.23**. The product was obtained as a colorless oil (87%, *de* > 95% as judged by ¹H-NMR spectroscopy).



¹H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, $J = 7.2, 0.6$, 4H), 7.55 – 7.37 (m, 6H), 5.79 – 5.61 (m, 1H), 5.03 (d, $J = 17.2$, 2H), 4.98 (d, $J = 10.2$, 2H), 3.58 (dd, $J = 9.7, 5.8$, 1H), 3.52 (dd, $J = 9.7, 6.4$, 1H), 2.28 (dq, $J = 14.0, 7.1$, 1H), 1.87 – 1.74 (m, 1H), 1.51 (ddd, $J = 23.8, 12.0, 7.4$, 1H), 1.15 (s, 9H), 1.05 (d, $J = 6.6$, 3H), 1.00 (d, $J = 6.6$, 3H); **¹³C NMR** (101 MHz, $CDCl_3$) δ 144.65, 135.64, 134.10, 129.48, 127.56, 112.57, 69.28, 40.43, 35.47, 33.40, 26.91, 21.33, 19.34, 16.79; **HRMS**-(APCI+) calculated for $C_{24}H_{35}OSi$ [$M + H$]⁺ 367.2457 Da, found 367.2452 Da.

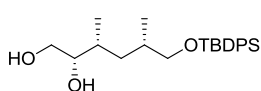
(2*S*,3*R*,5*S*)-6-((tert-butylidiphenylsilyl)oxy)-3,5-dimethylhexane-1,2-diol (2.33): The diol was



obtained in 79% yield and a dr ~ 6:1 (determined by ^{13}C -NMR spectroscopy) following a previously described procedure.^[23]

^1H NMR (400 MHz, CDCl_3) δ 7.67 (dd, $J = 7.8, 1.6, 4\text{H}$), 7.50 – 7.31 (m, 6H), 3.65 – 3.38 (m, 5H), 2.13 – 1.93 (OH, 1H), 1.79 – 1.69 (m, 1H), 1.63 – 1.47 (m, 3H), 1.06 (s, 9H), 0.95 (d, $J = 6.7, 3\text{H}$), 0.86 (d, $J = 6.7, 3\text{H}$); ^{13}C NMR (101 MHz, C_6D_6) δ major (*syn*) 136.11, 134.36, 130.00, 128.11, 75.41, 68.89, 65.44, 37.54, 33.41, 33.27, 27.22, 19.60, 18.32, 15.06; minor (*anti*) 136.11, 136.09, 134.38, 134.36, 130.00, 128.11, 128.10, 76.45, 68.71, 64.58, 36.90, 34.12, 33.66, 27.22, 19.60, 18.71, 16.13.

(2*S*,3*R*,5*S*)-6-((tert-butylidiphenylsilyl)oxy)-3,5-dimethylhexane-1,2-diol (2.33):

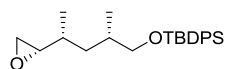


Tris(dibenzylideneacetone)diplatinum and ligand **L2.3** were prepared according to a previously reported procedure.^[18] To a flame-dried Schlenk flask, in a glovebox, were added $[\text{Pt}_2(\text{dba})_3]$

(0.025 eq, 6.71 mg, 0.006 mmol), ligand **L2.3** (0.05 eq, 10.0 mg, 0.013 mmol) and B_2pin_2 (1.05 eq, 66 mg, 0.26 mmol, recrystallized from pentane). THF (1.8 mL) was added and the Schlenk was closed, taken out of the glovebox and heated at 80 °C for 30 min. The reaction mixture was allowed to cool down and returned to the glovebox. The Schlenk flask was charged with **2.31** (90 mg, 0.25 mmol, prepared following the same procedure as compound **2.23**) dissolved in THF (0.7 mL, final concentration of substrate = 0.1 M). The Schlenk was again removed from the glovebox and heated at 60 °C for 14 h. The reaction was cooled down to 0 °C and the flask was charged with NaOH (2 mL, 3 M) and H_2O_2 (2 mL, 50% in water). The mixture was allowed to slowly reach rt and stirred for a total of 4 h. The flask was cooled down to 0 °C and a saturated solution of aq. $\text{Na}_2\text{S}_2\text{O}_3$ (2 mL) was added dropwise. The mixture was diluted with EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over MgSO_4 , filtered, and the solvent was evaporated. The crude product was purified using flash chromatography (pentane/EtOAc 4:1) to give **2.33** (74 mg, 75%, de > 95%) as a colorless oil.

^1H NMR (400 MHz, C_6D_6) δ 7.71 (dd, $J = 7.6, 1.5, 4\text{H}$), 7.30 – 7.22 (m, 6H), 3.60 (dd, $J = 9.8, 4.9, 1\text{H}$), 3.46 (m, 4H), 2.85 (br, 2H), 2.36 (br, 1H), 1.75 (m, 1H), 1.68 – 1.42 (m, 3H), 1.29 (m, 2H), 1.19 (s, 9H), 0.98 (d, $J = 6.6, 3\text{H}$), 0.84 (d, $J = 6.6, 3\text{H}$); ^{13}C NMR (101 MHz, C_6D_6) δ 136.11, 134.35, 130.00, 128.11, 75.30, 68.86, 65.38, 37.47, 33.38, 33.21, 27.20, 19.60, 18.30, 15.04; HRMS-(ESI+) calculated for $\text{C}_{24}\text{H}_{36}\text{O}_3\text{SiNa}$ $[\text{M} + \text{Na}]^+$ 423.2331 Da, found 423.2339 Da.

tert-butyl(((2S,4R)-2-methyl-4-((S)-oxiran-2-yl)pentyl)oxy)diphenylsilane (2.34): To a stirred

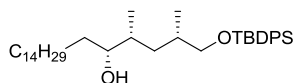


solution of diol **2.33** (71 mg, 0.18 mmol) in THF (2 mL) at 0 °C was added NaH (3 eq, 60% in mineral oil), and the mixture was allowed

to warm to rt. After 1 h, the mixture was cooled back to 0 °C and *N*-trisimidazole (1.05 eq., 62 mg) was added in two portions (ten minute difference). The mixture was again allowed to warm to rt and stirred for 1 h. The mixture was cooled to 0 °C and a saturated solution of aq. NH₄Cl (2 mL) and Et₂O (10 mL) were added. The aqueous layer was extracted three more times with Et₂O (10 mL). The organic layers were dried over MgSO₄, filtered and evaporated under reduced pressure. The crude product was purified using column chromatography (pentane/Et₂O 50:1) to afford **2.34** (50 mg, 74% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.62 (m, 4H), 7.48 – 7.34 (m, 6H), 3.50 (dd, *J* = 9.9, 5.6, 1H), 3.44 (dd, *J* = 9.9, 6.2, 1H), 2.77 – 2.69 (m, 1H), 2.67 – 2.56 (m, 1H), 2.50 (dd, *J* = 4.9, 2.8, 1H), 1.82 – 1.71 (m, 1H), 1.56 (ddd, *J* = 13.7, 7.9, 5.9, 1H), 1.38 – 1.30 (m, 2H), 1.07 (s, 9H), 1.01 (d, *J* = 6.7, 3H), 0.94 (d, *J* = 6.7, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 135.58, 133.88, 129.55, 127.58, 68.75, 57.17, 47.17, 37.48, 33.64, 33.09, 26.86, 19.24, 17.92, 17.44; **HRMS**- no exact mass could be obtained.

(2S,4R,5R)-1-((tert-butylidiphenylsilyl)oxy)-2,4-dimethylicosan-5-ol (2.35): The Grignard

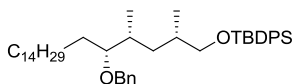


reagent was freshly prepared as a 0.15 M solution in THF starting from 1-bromotetradecane and magnesium turnings following a previously reported procedure.^[2c] (CuBr)₂

(0.15 eq, 5.2 mg, 0.018 mmol) was added to a stirred solution of epoxide **2.34** (46 mg, 0.12 mmol) in freshly distilled THF (1 mL). The solution was cooled down to –25 °C after which the Grignard reagent (3 eq, 0.36 mmol, 2.4 mL, 0.15 M solution in THF) was added dropwise over five minutes. After 1.5 h, TLC indicated complete consumption of the starting material and the reaction mixture was quenched with a saturated solution of aq. NH₄Cl (2 mL) and diluted with water (3 mL). Et₂O (10 mL) was added and the layers were separated. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified using column chromatography (pentane/Et₂O 20:1) to afford **2.35** (52 mg, 74%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.70 – 7.65 (m, 4H), 7.48 – 7.31 (m, 6H), 3.53 (dd, *J* = 9.8, 5.2, 1H), 3.49 – 3.43 (m, 2H), 1.89 – 1.71 (m, 1H), 1.58 – 1.49 (m, 1H), 1.48 – 1.36 (m, 4H), 1.34 – 1.22 (m, 26H), 1.07 (s, 9H), 0.96 (d, *J* = 6.7, 3H), 0.90 (t, *J* = 6.8, 3H), 0.83 (d, *J* = 6.5, 3H); **HRMS**-(ESI+) calculated for C₃₈H₆₄O₂SiNa [M + Na]⁺ 603.4573 Da, found 603.4568 Da.

(((2S,4R,5R)-5-(benzyloxy)-2,4-dimethylcosyl)oxy)(tert-butyl)diphenylsilane (2.36): To **2.35**

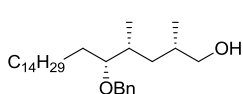


(104 mg, 0.18 mmol) in a flame-dried Schlenk flask equipped with a stirring bar, was added DCM (1 mL) and cyclohexane (2 mL). To the stirred solution was added benzyl 2,2,2-trichloroacetimidate (1.1 eq, 37 μ L, 0.20 mmol) and triflic acid (0.2 eq, 3.2 μ L, 0.036 mmol).

The cloudy solution was quenched after five hours with a saturated aqueous solution of NaHCO_3 (3 mL) and the product was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over MgSO_4 , filtered and the solvents were evaporated. The product was purified using column chromatography (pentane/ Et_2O 100:1) to afford **2.36** (69 mg, 57%), with traces of an unknown by-product, as a colorless oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.65 (dd, J = 4.0, 3.3, 4H), 7.44 – 7.21 (m, 11H), 4.43 (s, 2H), 3.52 (dd, J = 9.8, 4.9, 1H), 3.39 (dd, J = 9.8, 6.7, 1H), 3.20 – 3.10 (m, 1H), 1.78 – 1.70 (m, 2H), 1.57 – 1.47 (m, 2H), 1.43 – 1.35 (m, 2H), 1.32 – 1.20 (m, 26H), 1.04 (s, 9H), 0.95 (d, J = 6.6, 3H), 0.90 – 0.86 (t, J = 6.7, 3H), 0.85 (d, J = 6.9, 3H); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ 139.24, 135.63, 135.60, 134.04, 129.47, 128.39, 128.17, 127.76, 127.69, 127.63, 127.56, 127.23, 82.97, 71.81, 68.83, 36.74, 33.38, 33.00, 31.93, 30.78, 29.89, 29.72, 29.65, 29.37, 26.91, 26.23, 22.70, 19.31, 18.26, 18.26, 15.51, 14.13; **HRMS**-(ESI+) calculated for $\text{C}_{45}\text{H}_{71}\text{O}_2\text{Si}$ [$\text{M} + \text{H}$] $^+$ 671.5223 Da, found 671.5231 Da.

(2S,4R,5R)-5-(benzyloxy)-2,4-dimethylcosan-1-ol (2.37): To compound **2.36** (59 mg, 0.088

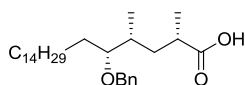


mmol) in THF (1 mL), was added TBAF (3 eq, 0.26 mmol, 1 M solution in THF). The reaction was stirred for 5 h after which TLC showed complete consumption of the starting material. The

solvent was evaporated, and the crude material was purified using column chromatography (pentane/DCM 1:1) to afford **2.37** as a colorless oil (30 mg, 79%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40 – 7.22 (m, 5H), 4.54, 4.49 (AB, J = 11.6, 2H), 3.48 (dd, J = 10.6, 4.8, 1H), 3.36 (dd, J = 10.6, 6.5, 1H), 3.29 – 3.16 (m, 1H), 1.93 – 1.75 (m, 1H), 1.68 – 1.61 (m, 1H), 1.58 – 1.51 (m, 2H), 1.47 – 1.37 (m, 2H), 1.36 – 1.21 (m, 26H), 0.96 – 0.85 (m, 9H); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ 139.17, 128.25, 127.78, 127.37, 82.58, 71.77, 67.95, 36.08, 33.27, 32.83, 31.92, 30.43, 30.31, 29.86, 29.69, 29.66, 29.65, 29.35, 26.27, 22.68, 17.79, 15.78, 14.11; **HRMS**-(ESI+) calculated for $\text{C}_{29}\text{H}_{52}\text{O}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$ 455.3865 Da, found 455.3870 Da.

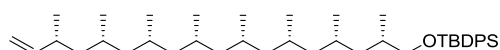
(2S,4R,5R)-5-(benzyloxy)-2,4-dimethylcosanoic acid (2.38): To a Schlenk flask charged with alcohol **2.37** (28.5 mg, 0.066 mmol) in a DMF/DCM mixture



(4:1, 1.3 mL), was added PDC (4 eq, 99 mg, 0.26 mmol). The reaction was stirred at rt for 16 h. After this period, an additional 1.5 eq of PDC was added. After 4 h, the starting material had disappeared as judged by TLC, and the reaction was quenched with water (5 mL), and the product was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed. The crude product was purified using column chromatography (5% Et₂O in toluene) to afford acid **2.38** (15 mg, 52%) as a white waxy solid.

¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.29 (m, 5H), 4.52 (s, 2H), 3.27 – 3.21 (m, 1H), 2.62 – 2.52 (m, 1H), 1.86 – 1.73 (m, 1H), 1.54 – 1.41 (m, 4H), 1.28 – 1.21 (m, 26H), 1.17 (d, *J* = 6.8, 3H), 0.96 – 0.85 (m, 6H); **HRMS**-(ESI+) calculated for C₂₉H₅₁O₃ [M + H]⁺ 447.3838 Da, found 447.3842 Da.

tert-butyl(((2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*)-2,4,6,8,10,12,14,16-octamethyloctadec-17-en-1-yl)oxy)diphenylsilane (2.23):

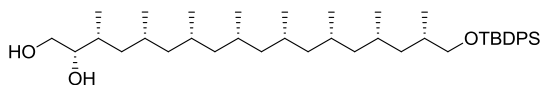


CuBr·SMe₂ (0.07 eq, 11.8 mg,

0.057 mmol) and (+)-TaniaPhos ligand (0.08 eq, 46.4 mg, 0.067 mmol) were added to a flame-dried Schlenk flask and dissolved in DCM (5 mL). The mixture was stirred for 10 min and then cooled to –75 °C. MeMgBr (1.2 eq, 337 μL, 1.01 mmol, 3 M solution in Et₂O) was added dropwise over a period of 10 minutes. Allylic bromide **2.22** (577 mg, 0.84 mmol) was then added dropwise over 20 minutes as a solution in DCM (final concentration of substrate = 0.15 M) using a syringe pump. The reaction was quenched after 14 h by the addition of MeOH (1 mL) and allowed to warm up to rt. A saturated solution of aq. NH₄Cl (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et₂O (3 x 5 mL) after which the combined organic layers were dried over MgSO₄, and filtered. All solvents were evaporated and the crude product was purified using column chromatography (pentane/Et₂O 100:1) to yield **2.23** (459 mg, 88%, *de* > 95%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J* = 7.8, 1.5, 4H), 7.47 – 7.31 (m, 6H), 5.61 (ddd, *J* = 17.3, 10.2, 8.2, 1H), 5.01 – 4.85 (dd, *J* = 18.2, 10.2, 2H), 3.52 (dd, *J* = 9.8, 5.0, 1H), 3.41 (dd, *J* = 9.8, 6.5, 1H), 2.23 (m, 1H), 1.80 – 1.65 (m, 1H), 1.63 – 1.45 (m, 7H), 1.44 – 1.24 (m, 3H), 1.24 – 1.11 (m, 7H), 1.05 (s, 9H), 0.98 (d, *J* = 6.7, 3H), 0.93 (d, *J* = 6.7, 3H), 0.88 – 0.75 (m, 21H); **¹³C NMR** (101 MHz, CDCl₃) δ 144.71, 135.62, 134.10, 129.45, 127.54, 112.56, 68.72, 45.54, 45.50, 45.39, 45.37, 43.88, 41.14, 35.64, 33.22, 27.72, 27.62, 27.58, 27.54, 27.38, 26.91, 21.63, 21.43, 21.36, 21.35, 21.15, 21.08, 20.53, 19.32, 18.22; **HRMS**-(ESI+) calculated for C₄₂H₇₀OSiNa [M + Na]⁺ 641.5094, found 641.5088.

(2*S*,3*R*,5*R*,7*R*,9*R*,11*S*,13*S*,15*S*,17*S*)-18-((*tert*-butyldiphenylsilyloxy)-3,5,7,9,11,13,15,17-octamethyloctadecane-1,2-diol (2.24): Tris(dibenzylideneacetone)diplatinum and ligand

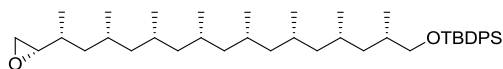


L2.3 were prepared according to a previously reported literature procedure.^[18] To a flame-dried

Schlenk flask, in a glovebox, was added [Pt₂(dba)₃] (0.05 eq, 11.9 mg, 0.011 mmol), ligand **L2.3** (0.105 eq, 18.3 mg, 0.023 mmol) and B₂pin₂ (3 eq, 166 mg, 0.65 mmol, recrystallized from pentane). THF (1.5 mL) was added, and the Schlenk flask was closed, taken out of the glovebox, and heated at 80 °C for 30 min. The reaction mixture was allowed to cool down and returned to the glovebox. The Schlenk flask was charged with terminal alkene **2.23** (135 mg, 0.22 mmol, dissolved in 0.7 mL THF, final concentration of substrate = 0.1 M). The Schlenk flask was again removed from the glovebox and heated at 60 °C for 14 h. The reaction was cooled down to 0 °C and the flask was charged with NaOH (2 mL, 3 M) and H₂O₂ (2 mL, 50% in water). The mixture was allowed to slowly reach rt and stirred for a total of 4 h. The flask was cooled down to 0 °C, and a saturated solution of aq. Na₂S₂O₃ (2 mL) was added dropwise. The mixture was diluted with EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over MgSO₄ and filtered. The solvent was evaporated, and the crude product was purified using flash chromatography (pentane/EtOAc 4:1) to give **2.24** (139 mg, 98%, *de* > 95%) as a colorless oil.

¹H NMR (300 MHz, CDCl₃) δ 7.69 (dd, *J* = 7.7, 1.5, 4H), 7.40 (m, 6H), 3.71 – 3.39 (m, 5H), 2.49 (br, 2H), 1.82 – 1.51 (m, 8H), 1.47 – 1.36 (m, 2H), 1.32 – 1.15 (m, 6H), 1.08 (s, 9H), 0.97 – 0.83 (m, 32H); ¹³C NMR (101 MHz, CDCl₃) δ 135.59, 134.06, 129.42, 127.52, 75.10, 68.68, 65.45, 45.47, 45.25, 45.21, 45.15, 45.00, 41.07, 40.96, 33.20, 32.86, 27.71, 27.66, 27.61, 27.58, 27.55, 27.52, 26.89, 21.52, 21.50, 21.47, 21.38, 21.20, 21.16, 19.29, 18.22, 15.03; ¹³C NMR (101 MHz, C₆D₆) δ 136.41, 134.74, 130.28, 75.44, 69.41, 66.14, 46.23, 46.07, 46.01, 45.82, 41.81, 41.78, 34.00, 33.58, 28.48, 28.45, 28.35, 28.19, 27.59, 25.38, 22.18, 22.16, 22.06, 21.89, 21.81, 19.97, 18.86, 15.75; HRMS-(ESI⁺) calculated for C₄₂H₇₂O₃SiNa [M + Na]⁺ 675.5148, found 675.5143.

tert-butyl(((2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*)-2,4,6,8,10,12,14-heptamethyl-16-((*S*)-oxiran-2-yl)heptadecyl)oxy)diphenylsilane (2.25): To a stirred solution of diol **2.24** (90.8 mg,



0.14 mmol) and cetrimide (0.1 eq, 5.07 mg, 0.014 mmol) in DCM (1 mL), was

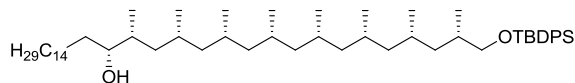
added an aq. solution of NaOH (50 eq, 1.6 mL, 25%) with vigorous stirring. A solution of

tosyl chloride (1.2 eq, 32 mg, 0.17 mmol) in DCM (600 μ L) was then added over a period of 10 min. The mixture was stirred for 60 min after which TLC showed complete consumption of starting material. The reaction was diluted with H₂O (5 mL) and DCM (5 mL). The layers were separated, and the aq. layer was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried (Na₂SO₄), filtered, and all volatiles were evaporated. The product was purified using column chromatography (pentane/Et₂O 50:1) to afford epoxide **2.25** (77 mg, 88%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, J = 7.7, 1.5, 4H), 7.47 – 7.31 (m, 6H), 3.52 (dd, J = 9.8, 5.0, 1H), 3.42 (dd, J = 9.8, 6.4, 1H), 2.78 (dd, J = 4.9, 4.0, 1H), 2.67 – 2.61 (m, 1H), 2.56 (dd, J = 5.0, 2.8, 1H), 1.78 – 1.70 (m, 1H), 1.63 – 1.51 (m, 7H), 1.43 – 1.35 (m, 4H), 1.23 – 1.16 (m, 7H), 1.06 (s, 9H), 1.03 (d, J = 6.4, 3H), 0.94 (d, J = 6.7, 3H), 0.87 (d, J = 6.5, 3H), 0.85 – 0.81 (m, 18H); **¹³C NMR** (101 MHz, CDCl₃) δ 135.61, 134.09, 129.44, 127.53, 68.70, 57.12, 47.24, 45.50, 45.30, 41.21, 41.10, 33.62, 33.21, 27.71, 27.58, 27.54, 27.49, 26.90, 21.44, 21.38, 21.35, 21.15, 21.06, 19.31, 17.96; **HRMS**-(ESI+) calculated for C₄₂H₇₁O₂Si [M + H]⁺ 635.5223, found 635.5218.

(16*R*,17*R*,19*R*,21*R*,23*R*,25*S*,27*S*,29*S*,31*S*)-32-((*tert*-butyldiphenylsilyl)oxy)-

17,19,21,23,25,27,29,31-octamethyltriacontan-16-ol (2.26): The Grignard reagent was freshly prepared as a 0.15 M solution in THF starting from 1-bromotetradecane and

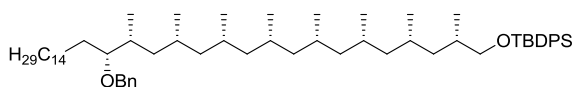


magnesium turnings following a previously reported procedure.^[11] Copper bromide dimethyl sulfide complex (0.15 eq, 1.5 mg, 7.1 μ mol) was added to a stirred solution of freshly distilled THF (0.5 mL). The solution was cooled down to –40 °C after which the Grignard reagent (3 eq, 0.14 mmol, 945 μ L, 0.15 M solution in THF) was added dropwise over 10 min. The solution was allowed to stir for 10 min, after which epoxide **2.25** (30 mg, 0.047 mmol) in THF (0.2 mL) was added over 10 min using a syringe pump. The reaction was monitored by TLC and quenched after 3 h with MeOH (1 mL). The mixture was allowed to warm to rt and a saturated aq. solution of NH₄Cl (5 mL) was added. The layers were separated and the aqueous layer was extracted with Et₂O (2 x 5 mL). The organic layers were pooled, dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified using column chromatography (pentane/Et₂O 20:1) to afford **2.26** (29 mg, 74%) as a colorless oil.

¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, J = 7.7, 1.5, 4H), 7.45 – 7.33 (m, 6H), 3.52 (dd, J = 9.8, 5.0, 2H), 3.42 (dd, J = 9.8, 6.5, 1H), 1.78 – 1.70 (m, 1H), 1.65 – 1.49 (m, 7H), 1.47 –

1.38 (m, 5H), 1.32 – 1.25 (m, 28H), 1.23 – 1.16 (m, 10H), 1.06 (s, 9H), 0.94 (d, $J = 6.7$, 3H), 0.92 – 0.77 (m, 24H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 135.61, 134.09, 129.43, 127.53, 74.31, 68.70, 45.50, 45.30, 45.28, 41.14, 41.10, 35.09, 34.91, 33.22, 31.93, 29.78, 29.70, 29.69, 29.68, 29.66, 29.64, 29.37, 27.72, 27.68, 27.65, 27.62, 27.58, 27.56, 26.90, 26.38, 22.70, 21.50, 21.48, 21.46, 21.38, 21.26, 21.16, 19.31, 18.23, 14.13, 14.03; **HRMS**-(APCI+) calculated for $\text{C}_{56}\text{H}_{100}\text{O}_2\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 855.7390, found 855.7385.

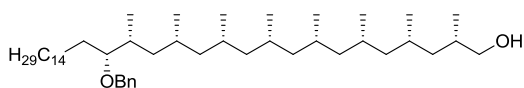
(((2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-17-(benzyloxy)-2,4,6,8,10,12,14,16-octamethyldotriacontyl)oxy)(tert-butyl)diphenylsilane (2.27):



To a Schlenk flask equipped with a stirring bar, was added alcohol **2.26** (26 mg, 0.031 mmol) and a 9:1 mixture of *c*-hexane/DCM (0.3 mL, 0.1 M). The solution was cooled to 0 °C, and benzyl 2,2,2-trichloroacetimidate (2 eq, 15.8 mg, 0.063 mmol) and trimethylsilyl trifluoromethanesulfonate (0.1 eq, 0.7 mg, 3.1 μmol) were added. The reaction was allowed to warm to rt and stirred until complete conversion was obtained according to TLC. The reaction was quenched with a saturated aq. NaHCO_3 solution (1 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 5 mL), and all organic layers were combined, dried over MgSO_4 , filtered and evaporated to dryness. The product was purified using column chromatography (pentane/ Et_2O 100:1) to afford benzyl ether **2.27** as a colorless oil with traces of an unidentified impurity (22 mg, 76%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.69 (dd, $J = 7.6$, 1.4, 4H), 7.47 – 7.30 (m, 11H), 4.53 (s, 2H), 3.54 (dd, $J = 9.8$, 5.0, 1H), 3.43 (dd, $J = 9.8$, 6.5, 1H), 3.29 – 3.22 (m, 1H), 1.87 – 1.81 (m, 1H), 1.78 – 1.72 (m, 1H), 1.66 – 1.51 (m, 7H), 1.48 – 1.37 (m, 5H), 1.36 – 1.15 (m, 36H), 1.08 (s, 9H), 0.96 (d, $J = 6.7$, 3H), 0.94 – 0.75 (m, 24H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 139.34, 135.61, 134.07, 129.44, 128.20, 127.58, 127.53, 127.24, 82.82, 71.81, 68.67, 45.46, 45.25, 45.23, 45.19, 41.06, 40.55, 33.20, 32.87, 31.93, 30.75, 29.90, 29.71, 29.67, 29.37, 27.91, 27.73, 27.68, 27.58, 27.52, 26.89, 26.84, 26.20, 22.70, 21.64, 21.54, 21.51, 21.48, 21.37, 21.16, 19.31, 18.24, 15.70, 14.14; **HRMS**-(APCI+) calculated for $\text{C}_{56}\text{H}_{100}\text{O}_2\text{SiNa}$ [$\text{M} + \text{Na}$] $^+$ 945.7860, found 945.7854.

(2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-17-(benzyloxy)-2,4,6,8,10,12,14,16-



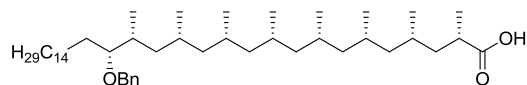
octamethyldotriacontan-1-ol (2.28): To a solution of compound **2.27** (42 mg, 0.045 mmol) in THF (455 μL , 0.1 M), was added TBAF (2 eq, 91 μL , 0.091 mmol, 1 M solution in THF). After completion, the

reaction was concentrated and the crude product was subjected to column chromatography. Primary alcohol **2.28** (28 mg, 90% based on integration in $^1\text{H NMR}$) was obtained as a colorless oil combined with siloxane as an inseparable side product.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.42 – 7.32 (m, 5H), 4.52 (s, 2H), 3.55 (dd, $J = 10.4, 4.8$, 1H), 3.37 (dd, $J = 10.2, 7.1$, 1H), 3.27 – 3.22 (m, 1H), 1.86 – 1.79 (s, 1H), 1.78 – 1.69 (m, 1H), 1.64 – 1.53 (m, 7H), 1.52 – 1.38 (m, 5H), 1.36 – 1.18 (m, 36H), 0.94 (d, $J = 6.7$, 3H), 0.92 – 0.78 (m, 24H); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ 139.33, 128.19, 127.69, 127.24, 82.85, 71.80, 68.12, 45.28, 40.91, 40.58, 33.07, 32.90, 31.92, 30.76, 29.89, 29.70, 29.66, 29.36, 27.76, 27.73, 27.67, 27.64, 27.57, 26.55, 26.19, 22.69, 21.62, 21.54, 21.49, 21.48, 21.33, 21.17, 17.72, 15.69, 14.12; **HRMS**-(ESI+) calculated for $\text{C}_{47}\text{H}_{89}\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 685.6862, found 685.6857.

(2*S*,4*S*,6*S*,8*S*,10*R*,12*R*,14*R*,16*R*,17*R*)-17-(benzyloxy)-2,4,6,8,10,12,14,16-

octamethyldotriacontanoic acid (2.18**):** To alcohol **2.28** (28 mg, 0.041 mmol) in acetonitrile



(234 μL), was added a buffer solution of KH_2PO_4 (175 μL , 0.1 M, pH 7), and the mixture was stirred vigorously. An

aq. solution of NaClO_2 (50 μL , 2.5 eq, 0.1 mmol, 2 M) and TEMPO (0.07 eq, 0.5 mg, 2.9 μmol) were added and the mixture was heated to 35 $^\circ\text{C}$. An aq. NaOCl (0.03 eq, 15 μL , 1.2 μmol , 0.5 %) solution was added and the reaction was stirred for 15 h after which it was quenched by the addition of a saturated aq. solution of Na_2SO_3 (0.3 mL). The mixture was carefully acidified to pH = 2, and Et_2O (4 mL) was added. After stirring vigorously for 30 min, the layers were separated, and the aqueous layer was extracted with Et_2O (2 x 4 mL). The combined organic layers were dried (MgSO_4), filtered, and all volatiles were evaporated. The crude product was purified using column chromatography (3% Et_2O in toluene). Carboxylic acid **2.18** (24 mg, 85%) was obtained as a colorless oil.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.47 – 7.29 (m, 5H), 4.52 (s, 2H), 3.29 – 3.15 (m, 1H), 2.65 – 2.49 (m, 1H), 1.86 – 1.73 (m, 2H), 1.64 – 1.53 (m, 7H), 1.51 – 1.40 (m, 5H), 1.28 – 1.21 (m, 36H), 1.19 (d, $J = 6.7$, 3H), 0.92 – 0.82 (m, 24H); **$^{13}\text{C NMR}$** (101 MHz, CDCl_3) δ 182.32, 139.33, 128.19, 127.71, 127.25, 82.86, 71.80, 45.36, 45.33, 45.27, 45.26, 45.05, 40.76, 40.57, 32.91, 31.93, 30.75, 30.30, 29.89, 29.71, 29.66, 29.37, 28.18, 27.92, 27.72, 27.64, 27.50, 27.27, 26.55, 26.19, 22.69, 21.59, 21.50, 21.45, 21.29, 20.93, 20.59, 19.01, 18.18, 15.71, 14.12; **HRMS**-(ESI+) calculated for $\text{C}_{47}\text{H}_{89}\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 685.6862, found 685.6857.

2.8 References

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