Synthesis of Methyl-Branched Lipids from Mycobacterium tuberculosis

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 2
Iterative Asymmetric Conjugate Addition Reactions in the Synthesis of Methyl Branched Lipids

In this chapter the development and application of iterative copper-catalyzed asymmetric conjugate addition (ACA) with Grignard reagents is described. It will focus on the construction of deoxypropionate motifs i.e. 1,3-methyl arrays, commonly found in natural products. The iterative method is based on the Josiphos/CuBr catalyzed conjugate addition of MeMgBr to unsaturated thioesters. The efficiency and selectivity are demonstrated in the synthesis of mycocerosic acid and phthioceranic acid, two multimethyl branched acids from Mycobacterium tuberculosis.*

2.1 Introduction

*Mycobacterium tuberculosis* (*M. tuberculosis*), the cause of tuberculosis, is still one of the predominant infectious agents. The rising number of human immunodeficiency virus (HIV) infected people is a major risk factor for the development of tuberculosis. Although efforts are made to control tuberculosis, mutations within the bacterium and irresponsible use of antibiotics are blocking a final stop to the disease.

The bacterium has an unusually thick cell wall, which consists partly of long-chain lipids, providing a highly hydrophobic barrier to antibiotics and other molecules. These lipids are potential therapeutic drug targets because they induce an immune response and play an important role in the build up and strength of the cell wall. For physiological and, especially, immunological studies, access to pure cell wall lipidic compounds is of paramount importance. However, in addition to regulatory restrictions, culturing of *M. tuberculosis* is difficult and purification of components from the lipid fraction is complicated. An effective synthetic route to these lipids is therefore highly desirable but has not been reported until now.

The cell wall of *M. tuberculosis* consists of many different waxes, phospholipids and lipids which often have long chain polydeoxypropionate fatty acids in their structure (Figure 1). Penta-acyl trehalose 3 (PAT), a disaccharide with five mycolipenic acyl side chains (chapter 3) is exclusively found in virulent strains of *M. tuberculosis* and plays a vital role in the outer membrane structure of the bacteria. Phthiocerol dimycocerosate (PDIM A) 1, a wax from the cell wall contains two tetramethyl-substituted fatty acids named mycocerosic acid (4, Figure 2). PDIM A is an important virulence factor of *M. tuberculosis*. Bacteria that lack the ability to produce PDIM A (by gene knockout) become less virulent or not virulent at all. Furthermore, proliferation in the lungs, spleen and liver of mice was lowered significantly.
Components of the cell wall are known to induce an immune response in the human body and are therefore potential candidates for vaccines or adjuvants.\textsuperscript{4} An important compound class in this respect, comprises the sulfolipids.\textsuperscript{4,5} Sulfolipids are acyl-substituted trehaloses containing a sulfate group. Sulfolipid-I (SL-I) (2, Figure 1) is of particular interest because it is known to induce an immune response.\textsuperscript{5,6} SL-I (2,3,6,6'-tetraacyltrehalose 2'-sulfate) and its acyl groups were characterized by Goren decades ago,\textsuperscript{7} and
shown to contain one palmitic acid, one phthioceramic acid (5), and two hydroxyphthioceramic acid (6) residues (Figure 1).

Figure 2: Mycocerosic, phthioceranic and hydroxyphthioceramic acid.

As a prelude to the enantioselective synthesis of PDIM A and SL-1 we decided to embark on the first total synthesis of mycocerosic and phthioceranic acid. As a strategy for the synthesis we used the copper-catalyzed 1,4-addition reaction in an iterative fashion.

2.2 Iterative 1,4-addition reactions to α,β-unsaturated thioesters for the construction of deoxypropionates

The application of the iterative copper-catalyzed 1,4-addition was demonstrated for the first time in the synthesis of (−)-lardolure (7, Scheme 1). In this synthesis, three iterative steps are executed starting with a 1,4-addition on thioester 8 in 92% yield and an ee of 96%. The thioester product 9 was reduced with Pd/C and Et3SiH (Fukayama conditions) to the aldehyde which was subsequently treated with Wittig reagent Ph3PCHCOEt to result in unsaturated thioester 10. The second catalytic asymmetric 1,4-addition yields syn-product 11 when the same enantiomer of the Josiphos ligand (16) is used (dr = 97.5 : 2.5). Subsequent reduction and olefination as before resulted in 12 in 80% yield over those two steps. The third methyl group was introduced under the same 1,4-addition conditions as before to provide 13. Sulfynyl ketone 14 was obtained by an addition reaction of thioester 13 with the lithium anion of (S)-methyl-p-tolylsulfoxide. Substrate-controlled diastereoselective reduction of the
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ketone with DIBAL-H resulted in β-hydroxysulfoxide 15 (de > 97%). Finally, desulfurization of 15 followed by formylation led to the final product (−)-lardolure (7).

Scheme 1: Asymmetric iterative 1,4-addition in the synthesis of (−)-lardolure (7).

2.3 Results and discussion

For the synthesis of mycocerosic and phthioceranic acid, a bifunctional substrate was designed. Most important requirement for this substrate was that it should be an unsaturated thioester that performs well in the enantioselective 1,4-addition (high yield, high enantioselectivity). A second requirement was that the substrate had a functionality next to the unsaturated system allowing further functionalization after the introduction
of the desired number of methyl groups. This functionality should be robust under 1,4-addition, reduction and olefination conditions (Scheme 2).

![Scheme 2](image)

**Scheme 2**: General scheme for the iterative 1,4-addition on unsaturated thioesters.

It had already been demonstrated that a benzyl-protected alcohol is tolerated in the 1,4-addition without affecting the enantioselectivity (Chapter 1). We were however worried about the stability of the benzyl ether under Fukuyama reduction\(^{10}\) conditions (Pd/C, Et\(_2\)SiH). Therefore we decided to change the protecting group into a bulky silyl group. Glycol (17) was monoprotected with TBDPSCI (\(t\)-butyldiphenylsilyl chloride) using an excess of glycol compared to the silyl chloride. Monoprotected diol 18 was obtained in 80% yield. The alcohol was oxidized to aldehyde 19 in refluxing EtOAc with 1.3 equiv. of IBX (idoxybenzoic acid). Crude aldehyde 19 was then dissolved in CH\(_2\)Cl\(_2\) and Wittig reagent 20 was added. The Wittig olefination favored the E-isomer over the Z-isomer (\(E:Z\), 90:10), and unsaturated thioester 21 was obtained in 78% yield over two steps.

![Scheme 3](image)

**Scheme 3**: Synthesis of bifunctional unsaturated ester substrate 21.

Substrate 21 proved to perform very well in the 1,4-addition with MeMgBr and the Josiphos/CuBr catalytic system (Scheme 4). Product 22 was obtained in 95% yield. It was found to be impossible to determine the
enantiomeric excess of 22 directly. However, desilylation of the product resulted in known lactone 23. Analysis of both racemic 23 and the product from the 1,4-addition by chiral GC showed that the enantioselective reaction resulted in 98% ee, the highest ee so far observed for the Josiphos/CuBr system on unsaturated thioesters. As the optical rotation of lactone 23 was known as well as its absolute configuration we could also establish that the use of (R,S)-Josiphos leads to (S)-22.

Scheme 4: Asymmetric 1,4-addition on 21 with MeMgBr and lactone formation for ee determination.

The obtained methyl-substituted thioester 22 could be selectively reduced to the corresponding aldehyde using Fukuyama reduction with Et₃SiH as the reducing agent or by treatment with DIBAL-H. Reductions with DIBAL-H were favored because we once observed a substantial amount of thiketal in the Fukuyama reduction. The formed aldehyde can react with ethanethiol to the corresponding thiketal under acidic conditions.

In the Wittig or Horner-Wadsworth-Emmons (HWE) olefination, the aldehyde is converted into unsaturated thioester 24 which can readily undergo a subsequent copper-catalyzed 1,4-addition. The Wittig olefination typically yields the unsaturated thioester with an E : Z ratio of 90 : 10. HWE olefination turned out to be more selective towards the E isomer with an E : Z ratio of >98 : 2. In addition, reaction times could be reduced from 16 h to 4-5 h (Chapter 6).

Depending on the enantiomer of 16 used in the second 1,4-addition (Scheme 5) to 24, either the syn (25) or the anti (26) product could be made. The same enantiomer of 16 as in the first step favors syn-product 25 and the anti-product is favored with ent-16 as the ligand.
Scheme 5: Second 1,4-addition for the construction of 1,3-dimethyl building blocks (syn or anti).

The two diastereomers 25 and 26 can be clearly distinguished by $^1$H-NMR (Figure 3). In the region between 2.0 and 2.6 ppm an ABX-pattern is visible. The two alfa-hydrogen’s of the thioester are diastereotopic (diastereotopic protons are those that, when one is substituted, lead to a pair of diastereomeric structures). Protons a and b are magnetically not equivalent and give different signals as can be clearly seen in Figure 3. Proton a couples with geminal proton b (14.4 Hz) and with proton x (the CH of the β-methyl substituent) resulting in a double doublet. The same is observed for proton b, which has the same coupling with proton a (14.4 Hz) and a coupling constant Jbx with x, which differs from Jax.

In case the two methyl groups from the 1,3-dimethyl product are in the anti fashion, the signals of a and b shift towards each other. The signals for the syn- and anti-product are separated and can be used to determine their diastereomeric ratio. Because the enantioselectivity is known for the first introduced methyl group, the selectivity of the second 1,4-addition can now be calculated (Figure 4).
**Figure 3:** $^1$H-NMR spectra of syn (25) and anti (26) products obtained via 1,4-addition reaction.

**Figure 4:** Ee calculation from syn-anti ratio’s in $^1$H-NMR.

To calculate the selectivity of the second 1,4-addition from the syn/anti ratio in $^1$H-NMR, we have to take in account that there is 1% of the unwanted R-enantiomer in the starting material. This 1% will react...
preferably to the anti-product if the same enantiomer of ligand 16 is used in the second 1,4-addition. To determine the selectivity of the formation of the anti-product we performed the 1,4-addition reaction with (ent)-16 on (S)-24 (Scheme 5). This results in a syn/anti ratio in $^1$H-NMR of 1 : 9. Because the selectivity for the anti-product is only 1 : 9, the 1% of the (R)-24 is negligible.

Starting with substrate 24, which consists of 99% of the S-enantiomer and 1% of the R-enantiomer (98% ee), and performing a second asymmetric 1,4-addition with ligand 16 (same as in the first 1,4-addition) results in a syn/anti ratio in $^1$H-NMR of 97 : 3. The syn-signal observed in $^1$H-NMR is the sum of the two syn-products S,R and R,S and the anti-signal is the sum of the anti-products S,S and R,R (Figure 4). The minor enantiomer will result in an anti/syn ratio of 9 : 1 as we established before and therefore we can now calculate all the diastereomeric ratio’s.

The minor enantiomer (R)-24 (1%) results in 0.9 of the R,R-(anti) and 0.1 of the R,S-(syn). We know that the sum $S,R_{-(syn)} + R,S_{-(syn)} = 97$ and $R,S_{-(syn)} = 0.1$ and therefore $S,R_{-(syn)}$ is 96.9. The sum of $S,S_{-(anti)} + R,R_{-(anti)} = 3$ and $R,R_{-(anti)} = 0.9$ and therefore $S,S_{-(anti)}$ is 2.1. The diastereomeric ratio of all diastereomers is 96.1(S,R) : 2.1(S,S) : 0.9(R,R) : 0.1(R,S).

Now it is possible to calculate the enantioselectivity of the overall reaction. The ratio of the set of syn-enantiomers (S,R and R,S) is 96.1 : 0.1 and results in an ee of 99.8%. This so-called statistical enantiomeric amplification effect rapidly results in ee’s of higher than 99.999% after 3 or 4 steps. It is also possible to calculate the enantioselectivity of the reaction using substrate (S)-24 if hypothetically we would have started with enantiopure (S)-24. This can be done by comparison of syn-(S,R) and anti-(S,S). The ratio is 96.9 : 2.1 and thus results in an ee of 96% (Figure 4).

The selectivity of every asymmetric 1,4-addition step could be determined by comparing the syn/anti ratio in the $^1$H-NMR spectra. Integration of the alpha hydrogens was used to determine the syn/anti ratio of the last two methyl groups introduced (Figure 5). The enantioselectivity of the third addition (27) (section 2.4.1) leads to >96% ee (the double doublet of the anti-product was just visible). As can be seen in Figure 5, selectivity goes up as more methyl groups are introduced. In the $^1$H-NMR of 27 (Figure 5) the anti-product is just visible.
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This substrate controlled syn-preference gets more profound in a longer all-syn deoxypropionate chain. The fourth methyl group (28) was introduced with 98% ee. For the fifth (29), sixth (30) and seventh (31) addition (section 2.4.2) the anti-product is no longer visible in $^1$H-NMR and the selectivity was >98% ee. This enhanced effect for syn-selectivity was even more profound in the total synthesis of hydroxy phthioceranic acid (chapter 6).

Figure 5: ABX-pattern in the $^1$H-NMR spectra of the iterative products 27, 28, 29, 30 and 31.

A plausible explanation for this preference is that syn-pentane interactions between the already present methyl group and the Cu$^{III}$ intermediate are minimized if the two groups are both syn. This is visualized in Figure 6 were both the syn and anti Cu$^{III}$-intermediates are presented on a diamond lattice. For the syn-product intermediate syn-pentane interactions are minimized and for the anti-product intermediate the interactions are maximized. Hanessian and co-workers found that the X-ray structure of a deoxypropionate substructure matched perfectly with the diamond lattice model and propose these intermediates in a similar system.
The enolate in the diamond lattice model is not drawn as a seven-membered ring between the bromomagnesium enolate and the σ-Cu\textsuperscript{18} atom as was suggested in chapter 1.\textsuperscript{16} The Z-enolate of the thioester (sulfur on the same side as the alkyl group) was found to be the reacting one in our trapping studies with aldehydes and explained the stereochemical outcome of those reactions, as is described in chapter 1.\textsuperscript{17} This, however, contradicts with the hypothesis of a seven-membered ring intermediate with E-geometry in the ring. For the reacting Z-enolate it is impossible to form the seven-membered ring (Figure 7). The diamond lattice model of the intermediate species is speculative, but does nicely match with the observed high preference for the all syn-product in the iterative 1,4-additions.

Figure 6: Syn and anti-product intermediates on a virtual diamond lattice, for clarification the ligand on copper is not presented.
2.3.1 Total synthesis of mycocerosic acid and 2,4,6,8-tetramethyl-decanoic acid.

Mycocerosic acid (4), one of the many methyl-branched fatty acids from *M. tuberculosis*, was first studied by Marks and Polgar in the fifties. In 1963 Polgar and Smith elucidated its absolute stereochemistry by degradation studies, which was established subsequently by the synthesis of mycocerosic acid starting from chiral pool compounds and via a route involving kinetic resolution. These studies established that the natural product was laevorotatory and possessed an all-R configuration. Recent studies showed that mycocerosic acid is produced by the enzyme mycocerosic acid synthase (MAS), Rainwater and Kolattukudy studied the biosynthesis of mycocerosic acid and found that the MAS was specific for methylmalonyl-CoA and would not incorporate malonyl-CoA into fatty acids.

We anticipated that the Cu/Josiphos catalyzed iterative conjugate addition of MeMgBr to unsaturated thioesters would be an excellent strategy for the total synthesis of enantiopure 4 (Scheme 6). The starting material should have a functionality at the terminus of the unsaturated thioester that is robust under the iterative reaction conditions (conjugate addition, Pd-catalyzed reduction, and Wittig reaction). For this reason we selected 65, an unsaturated thioester with a protected hydroxyl group, prepared from glycol in 3 steps. Substrate 21 gave excellent enantioselectivity (98% ee) and complete regioselectivity in the copper-catalyzed 1,4-addition with MeMgBr and 1 mol% of (ent)-16/CuBr (Scheme 6). Upon deprotection, the known lactone (ent)-23 was formed, which allowed confirmation of the absolute stereochemistry. Bifunctional building block (R)-22 was reduced to the corresponding aldehyde followed by a Wittig reaction to give
thioester R-24. The syn-selectivity of the second conjugate addition, leading to dimethyl thioester (ent)-25, could be established by $^1$H-NMR spectroscopy in comparison with anti dimethyl thioester (ent)-26, prepared using 16 (Figure 3). The ratio syn/anti was higher than 97 : 3. The reduction/olefination, 1,4-addition sequence was applied four times in an iterative procedure to arrive at the tetramethyl substituted compound (ent)-28 in ten steps with excellent selectivity and an overall yield of 21% from 21. Twofold reduction of thioester (ent)-28 with DIBAL-H resulted in alcohol 32, which was converted subsequently into 33 after treatment with TsCl. The introduction of the long alkyl chain was achieved by treatment of 33 with C$_{18}$H$_{37}$MgBr and 20 mol% of CuBr•SM$_2$ to yield 34, which was deprotected with TBAF to yield the tetramethyl substituted alcohol 35. Oxidation of 35 gave mycocerosic acid (4) in 15 steps with an overall yield of 12% (86% on average). The optical rotation ($-6.4^\circ$, $c = 0.94$, CHCl$_3$) of 4 is in accordance with the literature value for the isolated product ($-5.6^\circ$, $c = 8.9$, CHCl$_3$).
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Scheme 6: Total synthesis of mycocerosic acid.

To further demonstrate the versatility of this iterative synthetic approach we decided to synthesize the related tetramethyl-substituted fatty acid 36, found in the preen-gland wax of the graylag goose Anser anser (Scheme 7). An asymmetric total synthesis of 36 was recently reported by Negishi and co-workers.
Scheme 7: Synthesis of 2,4,6,8-tetramethyl-decanoic acid.

Treatment of tosylate 33 with excess LiAlH₄ gave silyl-protected alcohol 37 in high yield. Deprotection (38) and oxidation as described for mycocerosic acid gave 2,4,6,8-tetramethyl-decanoic acid 36 in 15 steps starting from 21 with an overall yield of 13%. Optical rotation (−28°, c = 0.69, CHCl₃) was in agreement with the literature value (−25°, c = 0.20, CHCl₃). Minor diastereomers were visible in the ¹³C-NMR spectrum of the final product reported by Negishi. We found no minor diastereomers, probably due to higher selectivity in the iterative steps and possible removal of traces of diastereomers in the chromatography steps.

2.3.2 Total synthesis of phthioceranic acid

Phthioceranic and hydroxyphthioceranic acid (5 and 6 Figure 2) are hepta- and octamethyl-branched dextrorotatory deoxypropionates, respectively, containing a palmitoyl unit and a hydroxy functionality at C17 for the latter. There is strong evidence that the stereochemistry at the methyl branches is all-L,⁴⁺,⁷ e.g., all-S for phthioceranic acid and 2S,4S,6S,8S,10R,12R,14R,16R for hydroxyphthioceranic acid. On the contrary, the absolute stereochemistry of tetramethyl-substituted laevorotatory mycocerosic acid has been determined as all-D (R) by degradation studies.⁴ In that study phthioceranic acid was compared to mycocerosic acid and all-S dextrorotatory mycolipenic acid (2,4,6-trimethyl-tetracos-2-enoic acid). More recent studies showed that mycocerosic acid is produced by the enzyme mycocerosic acid synthase (MAS), whereas phthioceranic and hydroxyphthioceranic acid are produced by a polyketide synthase, Pks2.¹,⁶ This accounts for the opposite stereochemistry observed. The biosynthesis of the mycolipenic acids is genetically closely related to that of the
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phthioceranic acids. The stereochemistry of the hydroxyl group in hydroxyphthioceranic acid was assumed to be D (R).

The synthesis of 5 starts with 21 which was submitted to an enantioselective 1,4-addition with MeMgBr, catalyzed by 1 mol% of 16•CuBr in t-BuOMe at −78°C. The corresponding thioester 22 was isolated with an excellent 95% yield and 98% ee. This conjugate addition reaction was followed by a two-step transformation of 22 into 24 via reduction of the thioester into its corresponding aldehyde and subsequent Wittig reaction with Ph₃PCHCOEt. By repeating this sequence of 1,4-addition, reduction and Wittig olefination we introduced all 7 methyl groups in a 1,3-syn-fashion with excellent stereoselectivity and high yield. Thus, heptamethyl-substituted thioester 39 was synthesized in 19 steps with 8% overall yield starting from 21. The diastereoselectivity of all iterative conjugate addition reactions was >96%, as calculated from the clearly distinguishable syn/anti isomers by ¹H-NMR.

Thioester 39 was reduced with DIBAL-H to alcohol 40 (via the isolated aldehyde in two steps), which was subsequently converted into tosylate 41 with 2 equivalents of TsCl and pyridine. The long aliphatic chain was introduced via a copper-catalyzed coupling reaction with C₁₄H₂₉MgBr (3 equiv.) and 20 mol% of CuBr•SMe₂. The resulting silyl ether 42 was deprotected with TBAF to give alcohol 43, which was finally oxidized to title compound 5 with catalytic RuCl₃•(H₂O), and NaIO₄ in 90% over two steps. The overall yield of the synthesis is 4% over 24 steps. No minor diastereomers of 5 could be observed by ¹H- or ¹³C-NMR, most probably as a result of the chromatography steps which remove traces of minor diastereomers. The optical rotation of synthetic 5 was +4.6 ([α]₀, c = 1.12, CHCl₃). In order to compare our material with the available literature data for the natural product, a sample of 5 was converted into the corresponding methyl ester. Its optical rotation, [α]₀ = +6.2° (c = 0.55, CHCl₃), is in agreement with the value reported for the isolated compound, which consists of a mixture of phthioceranic acid homologues ([α]₀ = +7.9° (c = 2.03, CHCl₃). The mass spectra (EI) of the methyl esters of both synthetic 5 and the natural product were compared and are in agreement (M = 564).
2.4 Conclusions

In summary, a highly efficient iterative strategy for the preparation of deoxypropionates has been developed. It gives access to all possible diastereomers since both syn and anti 1,3-polyethyl arrays are accessible. The methodology is illustrated by the preparation of three naturally occurring fatty acids, mycocerosic acid (4), 2,4,6,8-tetramethyldecanoic acid (36) and phthioceramic acid (5). The overall yield of these syntheses is such that these and related compounds can be prepared readily for biological studies.
2.5 Experimental

General remarks: All reactions were carried out under a nitrogen atmosphere using dried glassware. All solvents were dried and distilled before use according to standard procedures. t-BuOMe was purchased as anhydrous grade, stored on 4Å MS and used without further purification. Ligand 16 was generously provided by Solvias. CuBr•SMe₂ was purchased from Aldrich or Acros and used without further purification. Grignard reagent MeMgBr was purchased from Aldrich. Grignard reagents were titrated using s-BuOH and catalytic amounts of 1,10-phenanthroline.

Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by staining with Seebach’s reagent: a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL).

Mass spectra were recorded on a AEI-MS-902 mass spectrometer. ¹H- and ¹³C-NMR were recorded on a Varian AMX400 (400, 100.59 MHz, respectively) using CDCl₃ as solvent. 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). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). Enantiomer excess was determined by capillary GC analysis (ChiralDEX A-TA column (30 m x 0.25 mm) using a flame ionization detector and compared with racemic products.

General procedure for the catalytic asymmetric conjugate addition of Grignard reagents to α,β-unsaturated thioesters (procedure A)

Josiphos•CuBr (1 mol%, 29.1 mg) was dissolved in t-BuOMe (24 mL) and stirred at rt for 30 min under nitrogen. The mixture was cooled to −75 °C and MeMgBr (4.687 mmol, solution in diethyl ether) was added dropwise. After stirring for 10 min, a solution of thioester (3.906 mmol) in t-BuOMe (7 mL) was added via a syringe pump over 1-2 h. The reaction mixture was stirred at −75 °C for 16 h, then quenched by the addition of MeOH and allowed to warm to rt. Saturated aq. NH₄Cl solution was then added, the
phases were separated and the aqueous layer extracted with Et₂O. The combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by column flash chromatography.

**General procedure for the reduction and following olefination sequence.**

**Fukuyama reduction (procedure B):** To a stirred mixture of the thioester (2 mmol) and 10% Pd/C (5 mol%, 106.4 mg) in CH₂Cl₂ (4 mL) was added Et₃SiH (6 mmol, 958 µL) at rt under nitrogen. Stirring was continued at rt until the reduction was completed (10-30 min). The catalyst was filtered off through a path of Celite and washed with the solvent of the reaction. The filtrate was concentrated under reduced pressure and purified by flash chromatography to give the pure aldehyde which was used in the next step without complete removal of the eluent.

**DIBAL-H reduction (procedure C):** To a stirred mixture of the thioester (0.499 mmol) in CH₂Cl₂ or THF (7 mL) was added DIBAL-H (0.524 mmol, solution in CH₂Cl₂ or toluene) at –65 °C under nitrogen. Stirring was continued until the reduction was completed (3-5 h). The reaction was quenched with a saturated aq. solution of Rochelle’s salt (potassium sodium tartrate) and was stirred for 1 h at rt. 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 purified by flash chromatography to give the pure aldehyde which was used in the next step without complete removal of the eluent.

**Wittig olefination (procedure D):** A solution of the aldehyde (2 mmol) and Ph₃PCHCOSEt (2.6 mmol, 947.6 mg) in CH₂Cl₂ (20 mL) was stirred overnight at rt. The solution was concentrated under reduced pressure and the product was purified by flash chromatography to afford the desired α,β-unsaturated thioester.

**Horner-Wadsworth-Emmons olefination (HWE olefination) (procedure E):** To a stirred solution of (EtO)₂POCHCOSEt (3.062 mmol) in THF (17 mL) at 0 °C under nitrogen was added n-BuLi (2.297 mmol, solution in hexane). The reaction mixture was stirred for an additional 20 min. A solution of aldehyde (1.531 mmol) in THF (2 mL) was added dropwise and after addition the reaction mixture was slowly warmed to rt and was stirred for 8 h. The reaction mixture was quenched.
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with a saturated solution of aq. NH₄Cl. The phases were separated and the aqueous layer extracted with 3 portions of diethyl ether. The combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography to afford the desired α,β-unsaturated thioester.

(E)-4-(t-Butyl-diphenyl-silanyloxy)-but-2-enethioic acid S-ethyl ester (21)

ESS

was added to a stirred solution of 6 equiv. of ethane-1,2-diol (12.0 mL, 231 mmol) and 1.1 equiv of imidazole (2.88 g, 42.4 mmol) in 200 mL of THF under nitrogen atmosphere. The resulting mixture was stirred for 24 h at rt and quenched with 200 mL water followed by addition of 200 mL of diethyl ether. After phase separation and extraction of the aqueous phase with 3 portions of 200 mL of diethyl ether, the combined organic phases were dried over MgSO₄, concentrated under reduced pressure and purified by flash chromatography (eluent pentane/EtOAc 4:1) to afford 18 as a colorless oil (9.14 g, 79% yield). A solution of 18 (9.14 g, 30.5 mmol) and 1.3 equiv of iodoxybenzoic acid (IBX) (11.09 g, 39.61 mmol) in 200 mL of EtOAc was refluxed for 24 h and cooled down to rt. IBX and benzoic acid were filtered off through a path of Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure to give the aldehyde 19 (8.81 g, 97% yield) which was used in the next step without purification. A solution of 19 (8.81 g, 29.6 mmol) and Ph₂PCHCOEt (13.99 g, 38.42 mmol) in CH₂Cl₂ (150 mL) was heated at reflux for 24 h. The solution was concentrated under reduced pressure and purified by flash chromatography (pentane/ether 40:1) to afford α,β-unsaturated thioester 21 as a colorless oil (9.078 g, 80% yield). ¹H-NMR (400 MHz, CDCl₃): δ 7.67 (dd, J = 7.6, 1.2 Hz , 4H), 7.42 (m, 6H), 6.90 (dt, J = 15.2, 3.2 Hz, 1H), 6.55 (dt, J = 14.8, 2.4 Hz, 1H), 4.35 (m, 2H), 2.98 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.09 (s, 9H). ¹³C-NMR (100.6 MHz, CDCl₃): δ 190.07 (s), 142.70 (d), 135.40 (d), 132.86 (s), 129.86 (d), 127.80 (d), 126.73 (d), 62.77 (t), 26.74 (q), 23.18 (t), 19.24 (s), 14.76 (q). MS(El⁺) for C₁₈H₁₉O₂SSi: m/z(%) = 327 (71%) (M – t-butyl), 384 (100%) (M). HRMS(El⁺) calculated for C₁₈H₁₉O₂SSi 327.0875, found 327.0875.
(+)-(R)-4-(t-Butyl-diphenyl-silanyloxy)-3-methyl-thiobutyric acid S-ethyl ester ((R)-22)

TBDPSONO\text{O}SEt The title compound was prepared from thioester 21 (3.0 g, 7.81 mmol) following procedure A with (S,R)-Josiphos•CuBr complex. (58 mg, 0.078 mmol, 1 mol%) and methylmagnesium bromide (9.37 mmol, solution in diethyl ether). The product was obtained as a colorless oil (2.968 g, 95% yield, 98% ee, [α]_{D} = +8.0° (c = 1.2, CHCl_{3})). \text{1H-NMR} (400 MHz, CDCl_{3}): δ 7.66 (dd, J = 6.8, 1.4 Hz, 4H), 7.41 (m, 6H), 3.55 (dd, J = 10.0, 5.3 Hz, 1H), 3.46 (dd, J = 9.9, 6.3 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.83 (dd, J = 14.5, 5.3 Hz, 1H), 2.38 (dd, J = 14.5, 8.4 Hz, 1H), 2.28 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 1.15 (s, 9H), 0.98 (d, J = 6.6 Hz, 3H). \text{13C-NMR} (100.6 MHz, CDCl_{3}): 199.08 (s), 135.57 (d), 133.63 (s), 129.58 (d), 127.50 (d), 67.90 (t), 47.75 (t), 33.76 (d), 26.84 (q), 23.27 (t), 19.28 (s), 16.40 (q), 14.77 (q). MS(El+) for C_{19}H_{23}O_{2}SSi: m/z(%) = 343 (100%) (M – t-Butyl), MS(Cl+) for C_{19}H_{23}O_{2}SSi: m/z(%) = 418 (37.5%) (M + NH_{4}^+), 401 (100%) (M + H^+). HRMS(El+) calculated for C_{19}H_{23}O_{2}SSi (M – t-butyl) 343.1188, found 343.1183.

Ee and absolute configuration were determined by removal of the t-butyldiphenylsilyl group by TBAF resulting in lactone (ent)-23. The absolute configuration of lactone 23 has been previously reported. Lit: [α]_{D} = −24.7 (c = 1.7, MeOH) for the S-configuration. Found: [α]_{D} = +22. (c = 0.50, MeOH). Determination of enantiomeric excess was achieved by GC analysis [Chiraldex AT-A (30.0 m x 0.25 mm), 1.0 ml min^{-1}, initial temp. 50 °C then 5 °C min^{-1} to final temp. 170 °C, 19.7 min (minor), 19.9 (major) shows 98% ee).

(+)-(E)-(R)-6-(t-Butyl-diphenyl-silanyloxy)-5-methyl-hex-2-enethioic acid S-ethyl ester ((R)-24)

TBDPSONO\text{O}SEt The title compound was prepared from thioester (R)-22 (2.0 g, 5 mmol), 10% Pd/C (5 mol%, 267 mg) and Et_{3}SiH (2.41 mL, 15.0 mmol) following procedure B. The resulting aldehyde was used in the olefination step (procedure D) with Ph_{3}PCHCOSiEt (2.366 g, 6.50 mmol). The product was obtained as a colorless oil (1.491 g, 70% yield over 2 steps, [α]_{D} = +5.7° (c = 1.57, CHCl_{3})). \text{1H-NMR} (400 MHz, CDCl_{3}):

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δ 7.65 (d, J = 7.9 Hz, 4H), 7.41 (m, 6H), 6.87 (dt, J = 15.4, 7.6 Hz, 1H), 6.11 (dt, J = 15.5, 1.4 Hz, 1H), 3.53 (dd, J = 10.0, 5.4 Hz, 1H), 3.46 (dd, J = 10.0, 6.4 Hz, 1H), 2.95 (q, J = 7.4 Hz, 2H), 2.44 (m, 1H), 2.05 (m, 1H), 1.86 (m, 1H), 1.29 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H). 13C-NMR (100.6 MHz, CDCl3): 189.97 (s), 143.89 (d), 135.57 (d), 133.70 (s), 129.95 (d), 129.61 (d), 127.64 (d), 68.07 (t), 35.97 (t), 35.42 (d), 26.86 (q), 23.03 (t), 19.29 (s), 16.46 (q), 14.83 (q). MS(El+) for C21H25O3Si: m/z(%) = 369 (100%) (M – t-Butyl), MS(Cl+) for C25H24O3Si: m/z(%) = 444 (100%) (M + NH4+), 427 (15%) (M + H+). HRMS(El+) calculated for C21H25O3Si (M – t-butyl) 369.1345, found 369.1331.

(+)-(3S,5R)-6-(t-Butyl-diphenyl-silanyloxy)-3,5-dimethyl-hexanethioic acid S-ethyl ester ((ent)-25)

The title compound was prepared from thioester (R)-24 (969 mg, 2.275 mmol) following procedure A with (S,R)-Josiphos•CuBr complex. (16.8 mg, 0.023 mmol, 1 mol%) and methylmagnesium bromide (2.73 mmol, solution in diethyl ether). The product was obtained as a colorless oil (900 mg, 90% yield, syn/anti ratio by 1H-NMR = 97/3, d.r. calculated from syn/anti ratio = (3S,5R);(3R,5S):(3S,5S):(3R,5S) = 97:2:1:0. [α]D = +4.6° (c = 1.91, CHCl3)). 1H-NMR (400 MHz, CDCl3): δ 7.67 (dd, J = 7.7, 1.6 Hz, 4H), 7.41 (m, 6H), 3.50 (dd, J = 9.9, 5.5 Hz, 1H), 3.43 (dd, J = 9.9, 6.4 Hz, 1H), 2.87 (q, J = 7.4 Hz, 2H), 2.52 (dd, J = 14.4, 5.1 Hz, 1H), 2.25 (dd, J = 14.4, 8.8 Hz, 1H), 2.08 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.24 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 1.03 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H). 13C-NMR (100.6 MHz, CDCl3): 199.15 (s), 135.61 (d), 133.94 (s), 129.50 (d), 127.57 (d), 68.74 (t), 51.19 (t), 40.79 (t), 33.16 (d), 28.69 (d), 26.88 (q), 23.26 (t), 20.28 (q), 19.29 (s), 17.42 (q), 14.79 (q). MS(El+) for C25H25O3Si: m/z(%) = 385 (100%) (M – t-Butyl), MS(Cl+) for C25H24O3Si: m/z(%) = 460 (100%) (M + NH4+), 443 (12.5%) (M + H+). HRMS(El+) calculated for C25H24O3Si (M – t-butyl) 385.1658, found 385.1668.
(3R,5R)-6-(t-Butyl-diphenyl-silyloxy)-3,5-dimethyl-hexanethioic acid S-ethyl ester (26)

The title compound was prepared from thioester 24 (40 mg, 0.094 mmol) following procedure A with (R,S)-Josiphos•CuBr complex. (3 mg, 0.004 mmol, 5 mol%) and methylmagnesium bromide (0.12 mmol, solution in diethyl ether). The product was obtained as a colorless oil (38 mg, 90% yield, syn/anti ratio by $^1$H-NMR > 10/90, $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.67 (dd, $J = 7.7, 1.6$ Hz, 4H), 7.41 (m, 6H), 3.47 (m, 2H), 2.87 (q, $J = 7.5$ Hz, 2H), 2.47 (dd, $J = 14.4, 6.3$ Hz, 1H), 2.37 (dd, $J = 14.5, 7.7$ Hz, 1H), 2.10 (m, 1H), 1.73 (m, 1H), 1.28 (m, 1H), 1.25 (t, $J = 7.4$ Hz, 3H), 1.08 (m, 1H), 1.06 (s, 9H), 0.90 (d, $J = 6.6$ Hz, 6H). $^{13}$C-NMR (100.6 MHz, CDCl$_3$): 199.10 (s), 135.61 (d), 134.00 (s), 129.49 (d), 127.56 (d), 69.29 (t), 52.14 (t), 40.13 (t), 33.11 (d), 28.4 (d), 26.88 (q), 23.25 (t), 19.30 (s), 19.17 (q), 16.36 (q), 14.81 (q).

(+)-(E)-(5R,7R)-8-(t-Butyl-diphenyl-silyloxy)-5,7-dimethyl-oct-2-enethioic acid S-ethyl ester (44)

The title compound was prepared from thioester (ent)-25 (290 mg, 0.656 mmol), 10% Pd/C (5 mol%, 35 mg) and Et$_3$SiH (0.316 mL, 1.968 mmol) following procedure B. The resulting aldehyde was used in the olefination step (procedure D) with Ph$_5$PCHCOSiEt$_2$ (287 mg, 0.787 mmol). The product was obtained as a colorless oil (214 g, 70% yield over 2 steps, [α]$_D$ = +7.6° (c = 1.97, CHCl$_3$)).

$^1$H-NMR (400 MHz, CDCl$_3$): δ 7.66 (dd, $J = 7.7, 1.6$ Hz, 4H), 7.41 (m, 6H), 6.83 (dt, $J = 15.4, 7.6$ Hz, 1H), 6.08 (dt, $J = 15.5, 1.4$ Hz, 1H), 3.50 (dd, $J = 9.8, 5.3$ Hz, 1H), 3.42 (dd, $J = 9.8, 6.3$ Hz, 1H), 2.94 (q, $J = 7.4$ Hz, 2H), 2.18 (m, 1H), 1.92 (m, 1H), 1.69 (m, 2H), 1.39 (m, 1H), 1.28 (t, $J = 7.4$ Hz, 3H), 1.06 (s, 9H), 1.02 (m, 1H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H).

$^{13}$C-NMR (100.6 MHz, CDCl$_3$): 189.97 (s), 144.07 (d), 135.59 (d), 133.93 (s), 129.84 (d), 129.51 (d), 127.57 (d), 68.61 (t), 40.76 (t), 39.45 (t), 33.08 (d), 29.96 (d), 26.86 (q), 23.01 (t), 20.12 (q), 19.28 (s), 17.59 (q), 14.81 (q).

MS(EI+) for C$_{24}$H$_{30}$O$_2$SSi: m/z(%) = 411 (100%) (M – t-butyl), MS(Cl+) for C$_{28}$H$_{40}$O$_2$Si: m/z(%) = 486 (100%) (M + NH$_4^+$). HRMS(EI+) calculated for C$_{24}$H$_{30}$O$_2$SSi (M – t-Butyl): 411.1814, found 411.1812.
(**)-**(3S,5R,7R)**8-(t-Butyl-diphenyl-silyloxy)-3,5,7-trimethyl-octanethioic acid S-ethyl ester (27)

\[
\begin{align*}
\text{TBDPSO} & \quad \text{O} \quad \text{SET} \quad \text{The title compound was prepared from thioester 44 (211 mg, 0.451 mmol) following procedure A with (S,R<sub>7</sub>)-}
\end{align*}
\]

\[\text{Josiphos-CuBr complex (163.2 mg, 0.004 mmol, 1 mol%) and methylmagnesium bromide (0.541 mmol, solution in diethyl ether). The product was obtained as a colorless oil (185 mg, 85% yield, syn/anti ratio by 1H-NMR = >96/4, d.r. calculated from syn/anti ratio = (3S,5R,7R):(3R,S,5R,7R):(3S,5S,7R):(3S,5R,7S) = 95:2:2:1, diastereomers smaller than 0.04 were neglected, [α]<sub>D</sub> = +6.8º (c = 1.13, CHCl₃)). 1H-NMR (400 MHz, CDCl₃): \(\delta\) 7.67 (dd, \(J = 1.7, 7.7\) Hz, 4H), 7.41 (m, 6H), 3.46 (dd, \(J = 9.8, 5.1\) Hz, 1H), 3.41 (dd, \(J = 9.8, 6.5\) Hz, 1H), 2.87 (q, \(J = 7.4\) Hz, 2H), 2.52 (dd, \(J = 5.0, 14.3\) Hz, 1H), 2.23 (dd, \(J = 8.8, 14.3\) Hz, 1H), 2.10 (m, 1H), 1.72 (m, 1H), 1.49 (m, 1H), 1.35 (m, 1H), 1.25 (t, \(J = 7.4\) Hz, 3H), 1.21 (m, 1H), 1.06 (s, 12H), 0.94 (d, \(J = 6.7\) Hz, 3H), 0.92 (m, 2H), 0.91 (d, \(J = 6.5\) Hz, 3H), 0.84 (d, \(J = 6.5\) Hz, 3H). 13C-NMR (100.6 MHz, CDCl₃): 199.22 (s), 135.60 (d), 134.03 (s), 129.47 (d), 127.54 (d), 68.74 (t), 50.93 (t), 44.71 (t), 41.18 (t), 33.08 (d), 28.59 (d), 27.61 (d), 26.88 (q), 23.24 (t), 20.53 (q), 20.46 (q), 19.29 (s), 17.98 (q), 14.80 (q). MS(El+) for C₃₅H₃₃O₂Si: m/z(%) = 427 (100%) (M − t-butyl), MS(El+) for C₃₅H₃₃O₂Si: m/z(%) = 502 (100%) (M + NH₄⁺). HRMS(El+) calculated for C₃₅H₃₃O₂Si (M − t-butyl) 427.2127, found 427.2142.
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(**)-**(E)-(5S,7R,9R)-10-(t-Butyl-diphenyl-silyloxy)-5,7,9-trimethyl-dec-2-enethioic acid S-ethyl ester (45)

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\begin{align*}
\text{TBDPSO} & \quad \text{O} \quad \text{SET} \quad \text{The title compound was prepared from thioester 27 (1,500 g, 3.099 mmol), 10% Pd/C (5 mol%, 165 mg) and Et₃SiH (1.494 mL, 9.297 mmol) following procedure B. The resulting aldehyde was used in the olefination step (procedure D) with Ph₃PCHCOSeEt (1.466 g, 4.029 mmol). The product was obtained as a colorless oil (1.102 g, 70% yield over 2 steps, [α]<sub>D</sub> = +8.2º (c = 0.83, CHCl₃)). 1H-NMR (400 MHz, CDCl₃): \(\delta\) 7.67 (dd, \(J = 7.9, 1.6\) Hz, 4H), 7.40 (m, 6H), 6.86 (dt, \(J = 15.5, 8.0\) Hz, 1H), 6.09 (dt, \(J = 15.5, 1.4\) Hz, 1H), 3.51 (dd, \(J = 9.8, 5.2\) Hz, 1H), 3.42 (dd, \(J = 9.8, 6.4\) Hz, 1H), 2.95 (q, \(J = 7.4\) Hz, 2H), 2.21 (m, 1H), 1.90 (m, 1H), 1.72(m, 2H), 1.52 (m, 1H), 1.36(m, 1H),
\end{align*}
\]

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The title compound was prepared from thioester 45 (1.102 g, 2.161 mmol) following procedure A with (S,R,R)-Josiphos-CuBr complex. (15.9 mg, 0.022 mmol, 1 mol%) and methylmagnesium bromide (2.593 mmol, solution in diethyl ether). The product was obtained as a colorless oil (1.010 mg, 88% yield, syn/anti ratio by $^1$H-NMR = >96/4, d.r. calculated from syn/anti ratio = (3S,5S,7R,9R): (3R,5S,7R,9R): (3S,5S,7S,9R): (3S,5S,7R,9S) = 94:1:2:2:1. diastereomers smaller than 0.04 were neglected [J]D = +6.7° (c = 1.14, CHCl3). $^1$H-NMR (400 MHz, CDCl3): δ 7.68 (dd, J = 7.8, 1.6 Hz, 4H), 7.41 (m, 6H), 3.53 (dd, J = 9.8, 5.0 Hz, 1H), 3.43 (dd, J = 9.8, 6.4 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.56 (dd, J = 14.3, 5.0 Hz, 1H), 2.26 (dd, J = 14.3, 8.8 Hz, 1H), 2.12 (m, 1H), 1.74 (m, 1H), 1.54 (m, 2H), 1.38 (m, 1H), 1.26 (t, J = 7.4 Hz, 3H), 1.20 (m, 2H), 1.17 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.89 (m, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H). $^{13}$C-NMR (100.6 MHz, CDCl3): 199.24 (s), 135.61 (d), 134.04 (s), 129.44 (d), 127.52 (d), 68.69 (t), 50.93 (t), 45.48 (t), 44.46 (t), 41.15 (t), 33.16 (d), 28.63 (d), 27.55 (d), 27.43 (d), 26.88 (q), 23.25 (t), 20.92 (q), 20.75 (q), 20.55 (q), 19.30 (s), 18.18 (q), 14.81 (q). MS(El+) for C_{28}H_{41}O_{5}SSi: m/z(%) = 469 (100%) (M – t-butyl), MS(Cl+) for C_{28}H_{40}O_{5}SSi: m/z(%) = 453 (100%) (M + HN$_3$). HRMS(El+) calculated for C_{28}H_{41}O_{5}SSi (M – t-butyl) 469.2597, found 469.2590.
Iterative Asymmetric Conjugate Addition Reactions in the Synthesis of Methyl Branched Lipids


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\text{TBDPSO} \quad \text{OH}
\]

To a stirred mixture of (ent)-28 (99.0 mg, 0.188 mmol) in THF (3 mL) was added DIBAL-H (0.388 mL, 0.388 mmol, 1.0 M solution in CH\(_2\)Cl\(_2\)) at -20 °C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was quenched in 30 mL saturated aq. Rochelle solution (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted with three portions of 30 mL CH\(_2\)Cl\(_2\). The combined organic phases were dried over MgSO\(_4\) and concentrated under reduced pressure to yield crude aldehyde. The above reduction/work-up was repeated to yield crude alcohol 32 as a colorless oil which was purified by flash chromatography (pentane/ether 1:1) to afford 32 as a colorless oil (83.2 mg, 95% yield, \([\alpha]_D = +3.9^\circ\) (c = 1.17, CHCl\(_3\))). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.68 (dd, \(J = 7.8, 1.6\) Hz, 4H), 7.41 (m, 6H), 3.68 (m, 2H), 3.43 (dd, \(J = 9.8, 5.0\) Hz, 1H), 3.44 (dd, \(J = 9.8, 6.5\) Hz, 1H), 1.79-1.15 (m, 10H), 1.08 (s, 9H), 0.97-0.82 (m, 15H). \(^1\)C-NMR (100.6 MHz, CDCl\(_3\)): (135.60, 135.58) (d), (134.06, 134.02) (s), (129.44, 129.42) (d), 127.51 (d), 68.65 (t), 61.19 (t), 45.60 (t), 41.14 (t), 33.14 (d), 27.54 (d), 27.31 (d), 26.91 (d), 26.86 (q), 20.96 (q), 20.54 (q), 19.29 (s), 18.19 (q). MS(EI+) for C\(_{36}\)H\(_{46}\)O\(_2\)Si: m/z(%) = 586 (100%) (M + NH\(_4^+\)). HRMS(El+) calculated for C\(_{36}\)H\(_{46}\)O\(_2\)Si (M – t-Butyl) 411.2719, found 411.2699.

(+)-(35,5S,7R,9R)-Toluene-4-sulfonic acid 10-(t-butyl-diphenyl-silyloxy)-3,5,7,9-tetramethyl-decyl ester (33)

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\text{TBDPSO} \quad \text{OTs}
\]

To a stirred mixture of 32 (356 mg, 0.761 mmol) and pyridine (0.123 mL, 0.1.521 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added toslyl chloride (290 mg, 1.521 mmol) at rt under nitrogen, and the mixture was stirred for 24 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (pentane/ether 9:1) to afford 33 as a colorless oil (452 mg, 95% yield, \([\alpha]_D = +3.9^\circ\) (c = 1.17, CHCl\(_3\))). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.80 (d, \(J = 8.3\) Hz, 2H), 7.68 (dd, \(J = 7.8, 1.6\) Hz, 4H), 7.39 (m, 8H), 4.07 (m, 2H), 3.52 (dd, \(J = 9.8, 5.0\) Hz, 1H), 3.43 (dd, \(J = 9.8, 6.4\) Hz, 1H), 2.44 (s, 3H), 1.73 (m, 15H).
The Grignard reagent was freshly prepared as a 0.20 M solution in THF. Octadecyl bromide (400 mg, 1.20 mmol) in THF (3.0 mL) was added to a stirred solution of activated (iodine) magnesium tu rnings (43.7 mg, 1.80 mmol) and crushed glass in THF (3.0 mL). After 1 h at 45 °C the reaction mixture was cooled to rt and 0.5 ml of the Grignard solution was titrated by using sec-BuOH and catalytic amounts of 1,10-phenanthroline. To a stirred mixture of 33 (100 mg, 0.161 mmol) and CuBr•SMe2 (6.6 mg, 0.032 mmol, 20 mol %) in THF (2 mL) was added n-C18H37MgBr (2.415 mL, 0.483 mmol, 0.2 M) at 0 °C under nitrogen. The reaction mixture was warmed to rt and stirred for 24 h. After quenching with 2.0 mL of saturated aq. NH4Cl solution, 5 ml of diethyl ether was added. The phases were separated and the aqueous layer was extracted with three portions of 10 mL diethyl ether. The combined organic phases were dried over MgSO4 and concentrated under reduced pressure to yield crude 34, which was purified by flash chromatography (pentane) to afford 34 as a colorless oil (91 mg, 80% yield, $\alpha$D = +4.3° (c = 1.03, CHCl3)). 1H-NMR (400 MHz, CDCl3): δ 7.68 (dd, J = 7.8, 1.6 Hz, 4H), 7.40 (m, 6H), 3.52 (dd, J = 9.8, 5.0 Hz, 1H), 3.42 (dd, J = 9.8, 6.4 Hz, 1H), 1.80-1.10 (m, 45H), 1.06 (s, 9 H), 0.94 (d, J = 6.7 Hz, 3H), 0.92-0.78 (m, 15H). 13C-NMR (100.6 MHz, CDCl3): (135.64, 135.62) (d), (134.13, 134.10) (s), 129.43 (d), 127.25 (d), 66.74 (t), 45.78 (t), 45.08 (t), 41.26 (t), 36.43 (t), 33.19 (d), 31.94 (t), 30.07 (t), 29.99 (d), 29.77 (t), 29.71 (12°C), 29.67 (t), 29.37 (t), 27.63 (d), 27.44 (d), 26.89 (q), 22.70 (t), 21.09 (q), 20.99 (q), 20.61 (q), 19.31 (s), 18.17 (q), 14.12 (q). MS(EI+) for C44H72OSi: m/z(%) = 647 (88.5%) (M – t-butyl), MS(Cl+) for C43H39O5Si: m/z(%) = 565 (100%) (M + NH4+). HRMS(EI+) calculated for C43H39O5Si (M – t-butyl) 565.2808, found 565.2792.

(+)-(2R,4R,6R,8R)-t-Butyl-diphenyl-(2,4,6,8-tetramethyl-octacosyloxy)-silane (34)
C₄₈H₈₄OSi: m/z(%) = 722 (100%) (M + NH₄⁺). HRMS(El⁺) calculated for C₄₆H₇₅OSi (M – t-butyl) 647.5587, found 647.5609.

(+)-(2R,4R,6R,8R)-Tetramethyl-octacosan-1-ol (35)

To a stirred mixture of 34 (135 mg, 0.192 mmol) in THF (1 mL) was added TBAF (0.384 mL, 0.384 mmol, 1.0 M solution in THF) at rt under nitrogen, and the mixture was stirred for 5 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (pentane/ethanol 10:1) to afford 35 as a white solid (80 mg, 90% yield, [α]D = +5.9º (c = 1.21, CHCl₃)). ¹H-NMR (400 MHz, CDCl₃): δ ppm 3.55 (dd, J = 10.5, 4.9 Hz, 1H), 3.37 (dd, J = 10.5, 6.9 Hz, 1H), 1.78–1.73 (m, 1H), 1.62–1.57 (m, 2H), 1.51–1.42 (m, 1H), 1.34–1.16 (m, 42H), 1.05–0.82 (m, 18H).

¹³C-NMR (100.6 MHz, CDCl₃): 68.20 (t), 45.52 (t), 45.04 (t), 41.07 (t), 36.43 (t), 33.10 (d), 31.92 (t), 30.06 (t), 29.99 (d), 29.70 (13*C), 29.36 (t), 27.56 (d), 27.46 (d), 26.86 (t), 22.69 (t), 21.04 (q), 21.06 (q), 20.59 (q), 17.65 (q), 14.11 (q). MS(Cl⁺) for C₃₂H₆₆O: m/z(%) = 484 (100%) (M + NH₄⁺). HRMS(El⁺) calculated for C₃₂H₆₄ (M – H₂O) 448.5008, found 448.5003.

(–)-(2R,4R,6R,8R)-Tetramethyl-octacosanoic acid / mycocerosic acid (4)

To a stirred mixture of 35 (19 mg, 0.041 mmol) in 0.3 mL CCl₄, 0.3 mL CH₃CN and 0.6 mL H₂O was added RuCl₃(H₂O)₃ (1.0 mg, 0.005 mmol) and NaIO₄ (37 mg, 0.172 mmol) at rt under nitrogen. After 3 h the reaction mixture was poured in 2 mL CH₂Cl₂ and 0.5 mL water was added. The phases were separated and the aqueous layer was extracted with three portions of 5 mL CH₂Cl₂. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude 4, which was purified by flash chromatography (pentane/diethyl ether 9:1) to afford 4 as a white solid/oil (16.7 mg, 85% yield, product did not contain other diastereomers by ¹³C-NMR, most probably due to the removal of traces of other isomers during chromatography purification steps. [α]D = –
6.4° (c = 0.94, CHCl₃), literature value for the product isolated from M. tuberculosis: [α]²₁ = –5.6° (c = 8.9, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 2.56 (m, 1H), 1.76 (m, 1H), 0.97-1.80 (m, 45H), 0.78-0.95 (m, 17H) ppm. ¹³C-NMR (100.6 MHz, CDCl₃): 182.87 (s), 45.34 (t), 45.31 (t), 40.86 (t), 37.19 (d), 36.64 (t), 31.92 (t), 30.05 (t), 29.93 (d), 29.75 (t), 29.70 (12°C), 29.35 (t), 28.13 (d), 27.21 (d), 26.91 (t), 22.68 (t), 20.59 (q), 20.44 (q), 20.40 (q), 18.08 (q), 14.10 (q). MS(EI⁺) calculated for C₃₂H₆₄O₂: m/z(%) = 480 (63%) (M). HRMS(EI⁺) calculated for C₃₂H₆₄O₂: 480.4906, found 480.4904.

A small sample (1 mg) was converted into the methyl ester of 4 (treatment with trimethylsilyldiazomethane) for mass analysis to compare with literature values ¹⁹,2⁰α, MS(EI⁺) for C₃₃H₆₆O₂: m/z(%) = 494 (35%) (M).

(+)-(2R,4R,6R,8R)-t-Butyl-diphenyl-(2,4,6,8-tetramethyl-decyloxy)-silane (37)

To a stirred mixture of 33 (46 mg, 0.074 mmol) in THF (1.5 mL) was added LiAlH₄ (14.0 mg, 0.370 mmol) at rt under nitrogen. After 24 h the reaction mixture was quenched with MeOH and 1.0 mL of 1 M aq. HCl solution and 2.0 ml diethyl ether were added. The phases were separated and the aqueous layer was extracted with three portions of 3 mL diethyl ether. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude 37, which was purified by flash chromatography (pentane/diethyl ether 9:1) to afford 37 as a colorless oil (30 mg, 90% yield, [α]₀ = +4.7° (c = 0.93, CHCl₃)). ¹H-NMR (400MHz, CDCl₃): δ ppm 7.68 (dd, J = 7.8, 1.6 Hz, 4H), 7.41 (m, 6H), 3.53 (dd, J = 9.8, 5.0 Hz, 1H), 3.43 (dd, J = 9.8, 6.4 Hz, 1H), 1.75 (m, 1H), 1.54 (m, 2H), 1.39 (m, 3H), 1.22 (m, 3H), 1.07 (s, 9H), 0.95 (d, J = 6.7 Hz, 3H), 0.86 (m, 15H). ¹³C-NMR (100.6 MHz, CDCl₃): (135.64, 135.62) (d), (134.11, 134.08) (s), 129.44 (d), 127.53 (d), 68.70 (t), 45.79 (t), 44.57 (t), 41.22 (t), 31.88 (d), 31.52 (d), 28.72 (t), 27.46 (d), 27.43 (d), 26.88 (q), 21.06 (q), 20.99 (q), 20.05 (q), 19.31 (s), 18.18 (q), 11.15 (q). MS(EI⁺) for C₂₆H₃₅OSi: m/z(%) = 395 (100%) (M – t-butyl), MS(Cl⁺) for C₃₀H₄₈OSi: m/z(%) = 470 (100%) (M + NH₄⁺). HRMS(EI⁺) calculated for C₂₆H₃₅OSi (M – t-butyl) 395.2770, found 395.2779.
Iterative Asymmetric Conjugate Addition Reactions in the Synthesis of Methyl Branched Lipids

(+)-(2R,4R,6R,8R)-Tetramethyl-decan-1-ol (38)

\[
\text{HO-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{OH}
\]

To 37 (82 mg, 0.181 mmol) in THF (2 mL) was added TBAF (0.363 mL, 0.363 mmol, 1.0 M solution in THF) at rt under nitrogen, and the mixture was stirred for 3 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (pentane/diethyl ether 9:1) to afford 38 as a white solid (33.4 mg, 86% yield, \([\alpha]_D^\circ = +6.4^\circ\) (c = 1.09, CHCl_3)). \(^1\)H-NMR (400 MHz, CDCl_3): \(\delta\) ppm 3.53 (dd, \(J = 10.4, 4.9\) Hz, 1H), 3.36 (dd, \(J = 10.4, 6.9\) Hz, 1H), 1.73 (m, 1H), 1.57 (m, 2H), 1.47-1.14 (m, 6H), 1.04 (m, 2H), 0.97-0.78 (m, 17H). \(^13\)C-NMR (100.6 MHz, CDCl_3): 68.13 (t), 45.51 (t), 44.54 (t), 41.02 (t), 33.07 (d), 31.51 (d), 28.73 (t), 27.51 (d), 27.42 (d), 21.03 (q), 20.98 (q), 20.02 (q), 17.64 (q), 11.12 (q). MS(CI+) for C_{14}H_{30}O: m/z(%) = 232 (100%) (M + NH_4\(^+\)). HRMS(EI+) calculated for C_{14}H_{28}O (M – H_2O) 196.2191, found 196.2191.

(–)-(2R,4R,6R,8R)-Tetramethyl-decanoic acid (36)

\[
\text{HO-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{CH_2-} - \text{COOH}
\]

To a stirred mixture of 38 (8.0 mg, 0.037 mmol) in 0.080 mL CCl_4, 0.080 mL CH_3CN and 0.115 mL H_2O was added RuCl_3•(H_2O), (1.0 mg, 0.005 mmol) and NaIO_4 (33.7 mg, 0.150 mmol) at rt under nitrogen. After 3 h the reaction mixture was poured in 5 mL diethyl ether and 0.5 mL water was added. The phases were separated and the aqueous layer was extracted with three portions of 5 mL diethyl ether. The combined organic phases were dried over MgSO_4 and concentrated under reduced pressure to yield crude 36, which was purified by flash chromatography (pentane/diethyl ether 9:1) to afford 36 as a white solid (7 mg, 82% yield, \([\alpha]_D^\circ = -28^\circ\) (c = 0.69, CHCl_3)) lit: Negishi et al. \(^{25}\) \([\alpha]_D^{23} = -25.1^\circ\) (c = 0.2, CHCl_3). \(^1\)H-NMR (400 MHz, CDCl_3): \(\delta\) ppm 2.59 (m, 1H), 1.75 (m, 1H), 1.57 (m, 2H), 1.47-1.00 (m, 8H), 0.99-0.78 (m, 15H). \(^13\)C-NMR (100.6 MHz, CDCl_3): 182.95 (s), 45.41 (t), 44.85 (t), 40.88 (t), 37.21 (d), 31.53 (d), 28.98 (t), 28.16 (d), 27.25 (t), 20.60 (t), 20.44 (q), 18.09 (q), 11.18 (q). HRMS(EI+) calculated for C_{14}H_{26}O_2 228.2089, found 228.2100.
(--)-(5R,7R,9S,11S)-12-(t-Butyl-diphenyl-silanyloxy)-5,7,9,11-tetramethyl-dodec-2-enethioic acid S-ethyl ester (46)

The title compound was prepared from thioester 28 (1.000 g, 1.901 mmol), 10% Pd/C (5 mol%, 101 mg) and Et₃SiH (0.916 mL, 5.703 mmol) following procedure B. The resulting aldehyde was used in the olefination step (procedure D) with Ph₃PCHCOEt (0.920 g, 2.471 mmol). The product was obtained as a colorless oil (735 mg, 70% yield over 2 steps, [α]D = −7.2° (c = 1.08, CHCl₃)). ¹H-NMR (400 MHz, CDCl₃): δ 7.67 (dd, J = 7.9, 1.6 Hz, 4H), 7.40 (m, 6H), 6.87 (dt, J = 15.3, 7.8 Hz, 1H), 6.10 (dt, J = 15.4, 1.4 Hz, 1H), 3.52 (dd, J = 9.8, 5.0 Hz, 1H), 3.43 (dd, J = 9.8, 6.3 Hz, 1H), 2.95 (q, J = 7.4 Hz, 2H), 2.23 (m, 1H), 1.92 (m, 1H), 1.73 (m, 2H), 1.54 (m, 2H), 1.38 (m, 1H), 1.28 (t, J = 7.4 Hz, 3H), 1.18 (m, 2H), 1.06 (s, 9H), 0.94 (d, J = 6.7 Hz, 3H), 0.93-0.85 (m, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H). ¹³C-NMR (100.6 MHz, CDCl₃): 189.96 (s), 144.19 (d), 135.60 (d), 134.05 (s), 129.82 (d), 129.44 (d), 127.51 (d), 68.64 (t), 45.52 (t), 44.42 (t), 41.09 (t), 38.97 (t), 33.13 (d), 29.89 (d), 27.53 (d), 27.38 (d), 26.87 (d), 23.00 (t), 20.97 (q), 20.81 (q), 20.52 (q), 19.29 (q), 18.16 (q), 14.82 (q). MS(El+) for C₃₀H₄₃O₂Si: m/z(%) = 495 (100%, M – t-butyl), MS(Cl+) for C₃₅H₅₀O₂Si: m/z(%) = 570 (100%, M + NH₄⁺). HRMS(El+) calculated for C₃₀H₄₃O₂Si (M – t-butyl) 495.2753, found 495.2728.

(--)-(3R,5R,7S,9S,11S)-12-(t-Butyl-diphenyl-silanyloxy)-3,5,7,9,11-pentamethyl-dodecanethioic acid S-ethyl ester (29)

The title compound was prepared from thioester 46 (618 mg, 1.120 mmol) following procedure A with (R,S,E)-Josiphos•CuBr complex. (8.25 mg, 0.011 mmol, 1 mol%) and methylmagnesium bromide (1.344 mmol, solution in diethyl ether). The product was obtained as a colorless oil (559 mg, 90% yield, syn/anti ratio by ¹H-NMR = >98/2, d.r. calculated from syn/anti ratio = 68.
(3R,5R,7S,9S,11S):(3S,5R,7S,9S,11S):(3R,5S,7R,9S,11S):(3R,5R,7S,9R,11S):(3R,5R,7R,9S,11R) = 93:1:1:2:1, diastereomers less than 0.04 were neglected. [α]D = −5.3° (c = 1.10, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.68 (dd, J = 7.8, 1.6 Hz, 4H), 7.41 (m, 6H), 3.52 (dd, J = 9.7, 5.0 Hz, 1H), 3.42 (dd, J = 9.6, 6.4 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.56 (dd, J = 14.3, 5.0 Hz, 1H), 2.26 (dd, J = 14.2, 8.7 Hz, 1H), 2.12 (m, 1H), 1.74 (m, 1H), 1.53 (m, 3H), 1.39 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 1.18 (m, 3H), 1.06 (s, 9H), 0.98-0.85 (m, 4H) 0.95 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H).

13C-NMR (100.6 MHz, CDCl3): 199.29 (s), 135.61 (d), 134.10 (s), 129.44 (d), 127.52 (d), 68.67 (t), 50.94 (t), 45.51 (t), 45.22 (t), 44.42 (t), 41.11 (t), 33.20 (d), 28.67 (d), 27.66 (d), 27.47 (d), 27.34 (d), 26.89 (q), 23.26 (t), 21.15 (q), 21.09 (q), 20.82 (q), 20.58 (q), 19.31 (s), 18.23 (q), 14.82 (q). MS(El+) for C31H41O2SSi: m/z(%) = 511 (100%, M – t-Butyl), MS(Cl+) for C35H56O2SSi: m/z(%) = 586 (100%, M + NH4+). HRMS(El+) calculated for C31H41O2SSi (M – t-butyl) 511.3066, found 511.3047.


The title compound was prepared from thioester 29 (512 mg, 0.907 mmol) in THF and DIBAL-H (1.180 mL, 1.180 mmol, solution in toluene) following procedure C. The resulting aldehyde was used in the olefination step (procedure D) with Ph3PCHCOEt (430 mg, 1.180 mmol). The product was obtained as a colorless oil (372 mg, 69% yield over 2 steps, [α]D = −6.8° (c = 1.21, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.68 (dd, J = 7.8, 1.6 Hz, 4H), 7.40 (m, 6H), 6.88 (dt, J = 15.4, 8.0 Hz, 1H), 6.10 (dt, J = 15.5, 1.3 Hz, 1H), 3.52 (dd, J = 9.8, 5.0 Hz, 1H), 3.42 (dd, J = 9.8, 6.4 Hz, 1H), 2.95 (q, J = 7.4 Hz, 2H), 2.24 (m, 1H), 1.94 (m, 1H), 1.74 (m, 2H), 1.54 (m, 3H), 1.39 (m, 1H), 1.28 (t, J = 7.4 Hz, 3H), 1.19 (m, 4H), 1.06 (s, 9H), 0.97-0.92 (m, 3H), 0.95 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). 13C-NMR (100.6 MHz, CDCl3): 189.95 (s), 144.19 (d), 135.61 (d), 134.07 (s), 129.83 (d), 129.42 (d), 127.51 (d), 68.64 (t), 45.47 (t), 45.24 (t), 44.37 (t), 41.10 (t), 38.97 (t), 33.16 (d), 29.93 (d), 27.62 (d), 27.42 (d), 27.34(d), 26.87 (q), 23.00 (t), 21.19 (q), 21.05 (q), 20.87 (q), 20.54 (q), 19.29 (s), 18.19 (q), 14.81 (q). MS(El+) for
C$_2$H$_{49}$O$_2$SSi: m/z(%) = 537 (100%, M – t-Butyl), MS(Cl+) for C$_{37}$H$_{58}$O$_2$SSi: m/z(%) = 612 (100%, M + NH$_4$+). HRMS(El+) calculated for C$_{33}$H$_{49}$O$_2$SSi (M – t-butyl) 537.3222, found 537.3198.


The title compound was prepared from thioester 47 (250 mg, 0.421 mmol) following procedure A with (R,S$_e$)-Josiphos•CuBr complex. (3.1 mg, 0.004 mmol, 1 mol%) and methylmagnesium bromide (0.505 mmol, solution in diethyl ether). The product was obtained as a colorless oil (242 mg, 94% yield, syn/anti ratio by $^1$H-NMR was >98/2, d.r. calculated from syn/anti ratio = (3R,5R,7R,9S,11S,13S):(3S,5S,7R,9S,11S,13S):(3R,5R,7S,9S,11S,13S):(3S,5R,7R,9S,11S,13S):(3R,5R,7R,9S,11S,13S) = 92:1:1:0.2:1, diastereomers less than 0.04 were neglected. [a]$_D$ = − 4.92° (c = 1.10, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.68 (dd, J = 7.8, 1.6 Hz, 4H), 7.40 (m, 6H), 3.52 (dd, J = 9.8, 4.9 Hz, 1H), 3.42 (dd, J = 9.8, 6.4 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.56 (dd, J = 14.3, 5.0 Hz, 1H), 2.26 (dd, J = 14.3, 8.8 Hz, 1H), 2.12 (m, 1H), 1.74 (m, 1H), 1.54 (m, 4H), 1.40 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 1.22 (m, 4H), 1.06 (s, 9H), 0.97-0.78 (m, 5H) 0.95(d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H). $^{13}$C-NMR (100.6 MHz, CDCl$_3$): 199.31 (s), 135.62 (d), 134.08 (s), 129.43 (d), 127.52 (d), 68.64 (t), 50.92 (t), 45.47 (t), 45.25 (t), 45.14 (t), 44.40 (t), 41.04 (t), 33.18 (d), 28.67 (d), 27.67 (d), 27.49 (d), 27.43 (d), 27.35 (d), 26.88 (q), 23.26 (t), 21.29 (q), 21.23 (q), 21.13 (q), 20.82 (q), 20.57 (q), 19.29 (s), 18.22 (q), 14.81(q). MS(El+) for C$_{34}$H$_{53}$O$_2$SSi: m/z(%) = 553 (100%, M – t-butyl), MS(Cl+) for C$_{38}$H$_{62}$O$_2$SSi: m/z(%) = 628 (100%, M + NH$_4$+). HRMS(El+) calculated for C$_{33}$H$_{49}$O$_2$SSi (M – t-butyl) 553.3535, found 553.3516.

The title compound was prepared from thioester 30 (236 mg, 0.387 mmol) in CH₂Cl₂ and Dibal-H (0.503 mL, 0.503 mmol, solution in toluene) following procedure C. The resulting aldehyde was used in the olefination step (procedure D) with Ph₃PCHCOSEt (183 mg, 0.503 mmol). The product was obtained as a colorless oil (193 mg, 78% yield over 2 steps, [α]D = −4.7° (c = 0.72, CHCl₃)). ¹H-NMR (400 MHz, CDCl₃): δ 7.67 (dd, J = 7.7, 1.5 Hz, 4H), 7.40 (m, 6H), 6.87 (dt, J = 15.4, 7.1 Hz, 1H), 6.10 (dt, J = 15.5, 1.2 Hz, 1H), 3.52 (dd, J = 9.8, 5.0 Hz, 1H), 3.42 (dd, J = 9.8, 6.4 Hz, 1H), 2.94 (q, J = 7.4 Hz, 2H), 2.23 (m, 1H), 1.94 (m, 1H), 1.73 (m, 2H), 1.55 (m, 4H), 1.39 (m, 1H), 1.28 (t, J = 7.4 Hz, 3H), 1.20 (m, 4H), 1.06 (s, 9H), 0.96-0.77 (m, 5H) 0.94 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.5 Hz, 3H), 0.97-0.92 (m, 5H). ¹³C-NMR (100.6 MHz, CDCl₃): 189.95 (s), 144.17 (d), 135.62 (d), 134.11 (s), 129.86 (d), 129.43 (d), 127.52 (d), 68.68 (t), 45.51 (t), 45.28 (t), 45.26 (t), 44.40 (t), 41.10 (t), 39.00 (t), 33.21 (d), 29.97 (d), 27.71 (d), 27.52 (d), 27.48 (d), 27.43 (d), 26.89 (q), 23.01 (t), 21.31 (q), 21.30 (q), 21.12 (q), 20.90 (q), 20.56 (q), 19.30 (s), 18.21 (q), 14.82 (q). MS(El⁺) for C₃₆H₅₅O₂S₂Si: m/z(%) = 579 (100%, M – t-butyl), HRMS(El⁺) calculated for C₃₆H₅₅O₂S₂Si (M – t-butyl) 579.3692, found 579.3669.


The title compound was prepared from thioester 48 (185 mg, 0.291 mmol) following procedure A with (R,S₃)-Josiphos•CuBr complex. (2.15 mg, 0.003 mmol, 1 mol%) and methylmagnesium bromide (0.349 mmol, solution in diethyl ether). The product was obtained as a colorless oil (175 mg, 92% yield, syn/anti by ¹H-NMR was >98/2, d.r. calculated from syn/anti ratio = (3R,5R,7R,9S,11S,13S,15S):(3S,5R,7R,9S,11S,13S,15S):(3R,5S,7R,9S,11S,13S,15S):(3R,5R,7R,9S,11S,13S,15S):(3R,5R,7R,9R,11S,13S,15S):(3R,5R,7R,9R,11R,13
91:1:1:1:2:2:1, diastereomers less than 0.04 were neglected. [α]D = –5.5° (c = 1.05, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.68 (d, J = 7.8, 1.6 Hz, 4H), 7.40 (m, 6H), 3.53 (dd, J = 14.8, 9.8 Hz, 1H), 3.42 (dd, J = 9.8, 6.4 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.56 (dd, J = 14.3, 5.0 Hz, 1H), 2.27 (dd, J = 14.3, 8.7 Hz, 1H), 2.12 (m, 1H), 1.74 (m, 1H), 1.55 (m, 5H), 1.40 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 1.23 (m, 5H), 1.06 (s, 9H), 0.99-0.77 (m, 6H), 0.95 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.84 (broad d, J = 6.3 Hz, 6H), 0.82 (broad d, J = 6.5 Hz, 6H). 13C-NMR (100.6 MHz, CDCl3): 199.27 (s), 135.62 (d), 134.11 (s), 129.43 (d), 127.52 (d), 68.69 (t), 50.96 (t), 45.48 (t), 45.29 (t), 45.26 (t), 44.45 (t), 41.09 (t), 33.21 (d), 28.68 (d), 27.72 (d), 27.54 (3 x C, d), 27.46 (d), 26.89 (q), 23.26 (t), 21.41 (q), 21.36 (q), 21.26 (q), 21.15 (q), 20.84 (q), 20.57 (q), 19.30 (s), 18.21 (q), 14.81 (q), MS(El+) for C37H59O2Si: m/z(%) = 595 (100%, M – t-butyl), HRMS(El+) calculated for C37H58O2Si (M – t-butyl) 595.4005, found 595.4006.


To a stirred mixture of 31 (91.0 mg, 0.140 mmol) in CH2Cl2 (2 mL) was added DIBAL-H (0.182 mL, 0.182 mmol, 1.0 M solution in CH2Cl2) at –50 °C under nitrogen. Stirring was continued until the reduction was completed (3-4 h). The reaction mixture was quenched in 5 mL saturated aq. Rochelle solution (potassium sodium tartrate) and stirred for 30 min. The phases were separated and the aqueous layer was extracted with three portions of 10 mL CH2Cl2. The combined organic phases were dried over MgSO4 and concentrated under reduced pressure to yield crude aldehyde. The above reduction/work-up was repeated to yield crude alcohol 40 as a colorless oil which was purified by flash chromatography (pentane/ether 1:1) to afford 40 as a colorless oil (76 mg, 91% yield, [α]D = –4.7° (c = 0.86, CHCl3)). 1H-NMR (400 MHz, CDCl3): δ 7.70 (d, J = 6.4 Hz, 4H), 7.41 (m, 6H), 3.70 (m, 2H), 3.54 (dd, J = 9.78, 5.0 Hz, 1H), 3.44 (dd, J = 9.7, 6.4 Hz, 1H), 1.65 (m, 7H), 1.43 (m, 2H), 1.25 (m, 7H), 1.08 (s, 9H), 0.97 (d, J = 6.7 Hz, 3H), 0.94-0.81 (m, 6H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (broad d, J = 6.5 Hz, 6H), 0.84 (broad d, J = 6.5, 6H). 13C-NMR (100.6 MHz, CDCl3): 135.60 (d), 134.07 (s), 129.42 (d), 127.51 (d), 68.64
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(t), 61.19 (t), 45.47 (t), 45.32 (t), 45.26 (2 x C, t), 45.13 (t), 41.05 (t), 39.38 (t), 33.17 (d), 27.68 (d), 27.51 (2 x C, d), 27.46 (d), 27.41 (d), 26.91 (d), 26.88 (q), 21.43 (q), 21.35 (q), 21.32 (q), 21.14 (q), 20.99 (q), 20.56 (q), 19.28 (s), 18.21 (q). HRMS(EI+) calculated for C_{35}H_{57}O_{2}Si (M – t-butyldiphenyl-silanyloxy)-3,5,7,9,11,13,15-heptamethyl-hexadecyl ester

\[ \text{TBDPSO}_\text{-} \text{HeptaC}_{\text{35}}\text{Si}-\text{Ts} \]

To a stirred mixture of 40 (68 mg, 0.114 mmol) and pyridine (0.019 mL, 0.228 mmol) in CH_{2}Cl_{2} (2 mL) was added tosyl chloride (44.8 mg, 0.235 mmol) at rt under nitrogen, and the mixture was stirred for 24 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (pentane/ether 9:1) to afford 41 as a colorless oil (84.4 mg, 99% yield, \([\alpha]_D = -4.0^\circ (c = 0.40, \text{CHCl}_3)\)). \(^1\)H-NMR (400 MHz, CDCl_{3}): \(\delta 7.81 (d, J = 8.4 \text{ Hz}, 2H), 7.68 (d, d, J = 7.8, 1.6 \text{ Hz}, 4H), 7.39 (m, 8H), 4.08 (m, 2H), 3.53 (dd, J = 9.8, 4.9 \text{ Hz}, 1H), 3.43 (dd, J = 9.7, 6.4 \text{ Hz}, 1H), 2.45 (s, 3H), 1.74 (m, 2H), 1.55 (m, 4H), 1.34 (m, 4H), 1.17 (m, 5H), 1.07 (s, 9H), 0.95 (d, J = 6.7 \text{ Hz}, 3H), 0.91-0.77 (m, 24H). \(^13\)C-NMR (100.6 MHz, CDCl_{3}): 144.54 (s), 135.59 (d), 134.05 (s), 133.24 (s), 129.75 (d), 129.41 (d), 127.83 (d), 127.50 (d), 69.07 (t), 68.63 (t), 45.43 (t), 45.21 (t), 45.15 (t), 45.09 (t), 44.61 (t), 41.03 (t), 35.14 (t), 33.16 (d), 27.66 (d), 27.47 (2 x C, d), 27.36 (d), 27.23 (d), 26.86 (q), 26.61 (d), 21.60 (q), 21.39 (q), 21.33 (q), 21.23 (q), 21.12 (q), 20.83 (q), 20.00 (q), 19.28 (s), 18.19 (q). HRMS(EI+) calculated for C_{32}H_{63}O_{2}Si (M – t-butyldiphenyl-silanyloxy)-3,5,7,9,11,13,15-heptamethyl-hexadecyl ester

\[ \text{TBDPSO}_\text{-} \text{HeptaC}_{\text{35}}\text{Si-O-Butyl} \]

The Grignard reagent was freshly prepared as a 0.15 M solution in THF. 1-Bromo-tetradecane (152 mg, 0.548 mmol) was added to a stirred solution of activated (iodine) magnesium turnings (16 mg, 0.658 mmol) and crushed glass in THF (3.0 mL). After 1 h at 45 °C the reaction mixture was cooled to rt and 0.5 ml of the Grignard solution was titrated by using sec-BuOH and catalytic amounts of 1,10-phenanthroline. To a stirred mixture of 41
(82 mg, 0.110 mmol) and CuBr•SMe₂ (4.5 mg, 0.022 mmol, 20 mol%) in THF (2 mL) was added C₁₈H₃₇MgBr (2.200 mL, 0.330 mmol, 0.15 M) at 0 °C under nitrogen. The reaction mixture was warmed to rt and stirred for 24 h. After quenching with 2.0 mL of saturated aq. NH₄Cl solution, 5 ml of diethyl ether was added. The phases were separated and the aqueous layer was extracted with three portions of 10 mL diethyl ether. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure to yield crude 42, which was purified by flash chromatography (pentane) to afford 42 as a colorless oil (64 mg, 75% yield, [α]D = −8.7° (c = 0.30, CHCl₃)). ¹H-NMR (400 MHz, CDCl₃): δ 7.67 (dd, J = 7.8, 1.5 Hz, 4H), 7.40 (m, 6H), 3.52 (dd, J = 9.8, 4.9 Hz, 1H), 3.41 (dd, J = 9.8, 6.5 Hz, 1H), 1.74 (m, 1H), 1.51 (m, 6H), 1.26 (m, 32), 1.04 (s, 9H), 0.94 (d, J = 6.7 Hz, 3H), 0.90-0.77 (m, 24H). ¹³C-NMR (100.6 MHz, CDCl₃): 135.62 (d), 134.10 (s), 129.43 (d), 127.52 (d), 68.68 (t), 45.50 (t), 45.47 (t), 45.33 (2 x C, t) 45.02 (t), 41.09 (t), 36.40 (t), 33.18 (d), 31.92 (t), 30.05 (t), 29.99 (d), 29.75 (t), 29.70 (7 x C, t), 29.65 (t), 29.36 (t), 27.67 (d), 27.54 (2 x C, d), 27.51 (2 x C, d), 26.88 (q), 22.68 (t), 21.42 (q), 21.36 (q), 21.33 (q), 21.15 (q), 21.12 (q), 20.61 (q), 19.29 (s), 18.20 (q), 14.12 (t). HRMS(EI+) calculated for C₄₉H₈₅O(Si (M – t-butyl) 717.6370, found 717.6346.

(+)-(2S,4S,6S,8S,10S,12S,14S)-2,4,6,8,10,12,14-Heptamethyl-triacontan-1-ol (43)

To a stirred mixture of 42 (20 mg, 0.026 mmol) in THF (2 mL) at rt under nitrogen was added TBAF (0.078 mL, 0.078 mmol, 1.0 M solution in THF), and the mixture was stirred for 5 h. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (pentane/ethanol 10:1) to afford 43 as a white solid containing traces of siloxane. (20 mg, crude, [α]D = −2.5° (c = 0.24, CHCl₃)). ¹H-NMR (400 MHz, CDCl₃): δ 3.55 (dd, J = 10.3, 4.9 Hz, 1H), 3.37 (dd, J = 10.4, 6.9 Hz, 1H), 1.72 (m, 1H), 1.58 (m, 3H), 1.51-1.12 (m, 40H), (m, 30H). HRMS(EI+) calculated for C₃₇H₇₄ (M – H₂O) 518.5790, found 518.5778.
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\((+)-(2S,4S,6S,8S,10S,12S,14S)-2,4,6,8,10,12,14-\text{Heptamethyl-triacontanoic acid (5)}\)

To a stirred mixture of crude 43 (20 mg, 0.026 mmol) in 0.6 mL CCl\(_4\), 0.6 mL CH\(_3\)CN and 1.2 mL H\(_2\)O was added RuCl\(_3\)•(H\(_2\)O)\(_x\) (1.0 mg, 0.005 mmol) and NaIO\(_4\) (24 mg, 0.109 mmol) at rt under nitrogen. After 3 h the reaction mixture was poured in 2 mL CH\(_2\)Cl\(_2\) and 0.5 mL water was added. The phases were separated and the aqueous layer was extracted with three portions of 5 mL CH\(_2\)Cl\(_2\). The combined organic phases were dried over MgSO\(_4\) and concentrated under reduced pressure to yield crude 5, which was purified by flash chromatography (pentane/diethyl ether 9:1) to afford 5 as a colorless oil (13 mg, 90% yield. The product did not contain other diastereomers according to \(^{13}\)C-NMR, most probably due to chromatography steps. \([\alpha]_D = +4.6^\circ\ (c = 1.12, \text{CHCl}_3)\), \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.59 (m, 1H), 1.77 (m, 1H), 1.57 (m, 4H), 1.50-0.94 (broad m, 34H), 1.19 (d, \(J = 6.9\) Hz, 3H), 1.10-0.96 (m, 4H), 0.94-0.79, (br, 27H). \(^{13}\)C-NMR (100.6 MHz, CDCl\(_3\)): 182.55 (s), 45.48 (t), 45.42 (2 x C, t), 45.08 (t), 45.05 (t), 40.72 (t), 37.16 (d), 36.43 (t), 31.92 (t), 30.05 (t), 29.98 (d), 29.75 (t), 29.69 (7 x C, t), 29.65 (t), 29.35 (t), 28.16 (d), 27.48 (2 x C, d), 27.43 (d), 27.24 (d), 26.85 (t), 22.68 (t), 21.28 (q), 21.21 (q), 21.12 (q), 20.85 (q), 20.59 (q), 20.54 (q), 18.13 (q), 14.11 (q). HRMS(EI+) calculated for C\(_{37}\)H\(_{74}\)O\(_2\): m/z(%) = 550.5689, found 550.5682.

A small sample (5.4 mg) was converted into the methyl ester of 5 (treatment with trimethylsilyldiazomethane) for optical rotation and mass analysis to compare with literature values.\(^7\)\(^c\)

\(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.66 (s, 3H), 2.58 (m, 1H), 1.77-1.39 (broad m, 5H), 1.30-1.08 (broad m, 38H), 1.05-0.74 (broad m, 27H). MS(EI+) for C\(_{38}\)H\(_{78}\)O\(_2\): m/z(%) = 564 (77%, M). Measured optical rotation: \([\alpha]_D = +6.2^\circ\ (c = 0.55, \text{CHCl}_3)\), literature value for mixture of homologues of phthioceranic methyl ester: \([\alpha]_D = +7.9^\circ\ (c = 2.03, \text{CHCl}_3)\).
2.6 References


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13 The integrals of the diastereomers were used to determine the diastereomeric ratio. The relaxation time in the \(^1\)H-NMR measurement was set at a value were both diastereomers relaxed completely between two pulses.