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Synthesis of Methyl-Branched Lipids from Mycobacterium tuberculosis

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Chapter 6
Total Synthesis and Stereochemical Elucidation of Hydroxyphthioceranic Acid

In this chapter the synthesis of hydroxyphthioceranic acid is described. Copper-catalyzed asymmetric allylic alkylation and iterative conjugate addition reactions are key strategic elements in the synthesis. The synthetic acid is compared to the natural product isolated from Mycobacterium tuberculosis and its configuration is established by comparison of spectroscopic and chromatographic data.
6.1 Introduction

Hydroxyphthioceranic acid, an octamethyl-branched acid with a propionate substructure in the chain (Figure 1) is found in cell wall components of *Mycobacterium tuberculosis* (*M. tuberculosis*) such as sulfolipid I (SL-I, 1) and diacylated sulfoglycolipid (acyl2SGL, 2).

SL-I is predominantly expressed in virulent strains of *M. tuberculosis* and is known to induce T-cell responses in the human body and is therefore of great interest for a possible novel vaccine against *M. tuberculosis*. The structure of SL-I was resolved in the seventies by Goren and co-workers.\textsuperscript{1a,b,c,d} It is comprised of a trehalose 2-sulfate core with two hydroxyphthioceranic acid residues at the 6- and 6'-position, one phthioceranic acid at the 3'-position and one palmitic or stearic acid at the 2'-position. Hydroxyphthioceranic and phthioceranic acid are uniquely found in the sulfatides of *M. tuberculosis*. Another sulfatide is acyl2SGL, discovered and characterized by Gilleron et al in 2004.\textsuperscript{2} This diacylated trehalose 2-sulfate contains one hydroxyphthioceranic acid at the 3'-position and a palmitic or stearic acyl-substituent at the 2'-position. Synthetic analogues of acyl2SGL with different acylchains were recently published and also showed T-cell response but were less biological active compared to the natural product containing hydroxyphthioceranic acid.\textsuperscript{3} Hydroxyphthioceranic acid is positioned at the 3'-position as supposed to the 6 and 6'-position in SL-I and this questions the assignment of the acylchains in SL-I.

Phthioceranic (Chapter 2) and hydroxyphthioceranic acid are produced by a polyketide synthase, Pks2 and belong to the dextrorotatory acids.\textsuperscript{4} All methyl substituents are assumed to be of the L-configuration which means all syn and with an absolute configuration of 2S,4S,6S,8S,10S,12S,14S for phthioceranic acid and 2S,4S,6S,8S,10R,12R,14R,16R for hydroxyphthioceranic acid (the priority changes because of the hydroxy group at the 17-position). The configuration of the hydroxyl-bearing carbon group is unknown but was suggested to be R, resulting in a syn methyl-hydroxy relationship as depicted in Figure 1.\textsuperscript{5,6}

For immunological studies and potential vaccine development, access to pure SL-I and acyl2SGL 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. In addition to the synthesis of phthioceranic acid\(^{28}\) (chapter 2) we embarked on the first total synthesis of hydroxyphthioceranic acid and the elucidation of the stereochemistry of the 17-hydroxy group as part of the construction of SL-I (1) and acyl\(_2\)SGL (2).

![Figure 1: Hydroxyphthioceranic acid containing components from *Mycobacterium tuberculosis*: SL-I (1) and acyl\(_2\)SGL (2).](image)

6.2 Retrosynthetic analysis

The retrosynthetic analysis of hydroxyphthioceranic acid can be divided into three parts. Part A (Scheme 1) consists of the construction of the long aliphatic C-15 side chain and the hydroxy-stereocenter. We envisioned the use of a hetero asymmetric allylic alkylation (h-AAA) reaction on 3, by a methodology recently developed in our group.\(^7\) This would stereoselectively create the hydroxyl-stereocenter and the aliphatic chain in one step (4). The resulting terminal olefin 4 can be further functionalized to thioester 5 by a ruthenium-catalyzed cross-metathesis reaction with S-
ethyl acrylate as the metathesis partner, this methodology was published recently by our group (see also chapter 4).

Scheme 1: Retrosynthetic analysis of hydroxyphthioceranic acid (P = protecting group).

In part B of the retrosynthetic analysis, the eight methyl substituents can be incorporated by an iterative 1,4-addition sequence which is described in chapter 2. After the introduction of the all-syn methyl branched product 6, the thioester functionality has to be shortened by one carbon (part C) in order to get the alpha-branched acid as supposed to beta-branched thioester 6. Thioester 6 can selectively be converted into the methyl ketone 7 by organocuprate addition. Baeyer-Villiger oxidation would result in acetate ester 8 and thereby the chain is reduced by one carbon atom.
Hydrolysis followed by oxidation and deprotection would result in hydroxyphthioceranic acid.

6.3 Results and discussion

6.3.1 Synthesis of hydroxyphthioceranic acid: first approach

Our initial approach was to introduce the long alkyl chain and the hydroxyl group in one step by a copper-catalyzed hetero asymmetric allylic alkylation (h-AAA) reaction with a Grignard reagent. This previously reported strategy was found to be highly selective to a variety of substrates and Grignard reagents. Substrate 3 was prepared as was reported from benzoyl bromide and acrolein. (-)-(S,S)-Taniaphos was used as the ligand and freshly prepared C_{15}H_{31}MgBr as the Grignard reagent. Benzoyl ester 4 was obtained in 85% yield. The enantiomeric excess was determined after hydrolysis to allylic alcohol 10. The Mosher ester of allylic alcohol was used to determine the enantiomeric excess. The diastereomeric ratio of the Mosher esters was found to be > 99 : 1 by 'H-NMR. Unsaturated thioester 11 was obtained after cross-metathesis of allylic alcohol 10 and S-ethyl acrylate catalyzed by Hoveyda-Grubbs second-generation catalyst in 60% yield. Silyl ether 12 was obtained in 86% yield from 11 after treatment with t-butyldiphenylsilyl triflate (TBDPSOTf) (in situ generated from TBDPSCI and AgOTf). Asymmetric copper-catalysed 1,4-addition with methylmagnesium bromide as described in chapter 2 did not yield the product, however, and the starting material was recovered. Because of a possible match, mismatch effect of the chiral substrate and the ligand, both enantiomers of Josiphos ligand were tested. However, neither 13 or 14 was obtained and starting material was recovered.
Because substrate 12 is much more hindered compared to the substrate described in chapter 2 and thereby likely less reactive, we attempted the 1,4-addition reaction at higher temperatures. Either no reaction occurred or the undesired 1,2-addition product was obtained. We have previously reported the use of sterically demanding substrates with an i-propyl group in the gamma-position without any problems when tol-Binap/Cul was used as the catalytic system. Substrate 12 was tested under these conditions and the product was obtained in poor yield and moderate syn/anti stereoselectivity, 5/1 for (R)-tol-BINAP and 3/1 for (S)-tol-BINAP, determined by 1H-NMR of the crude lactone 22 obtained after ring closure upon treatment with TBAF (*vide infra*).

To decrease steric hindrance we switched to a less bulky protecting group for the alcohol (Scheme 3). Benzilation of allylic alcohol 10 to 15 followed by cross metathesis with S-ethyl acrylate yielded 16 in 60% over two steps. Subjecting substrate 16 under ACA conditions resulted surprisingly in
almost quantitative formation of reduced product 17, without the benzyloxy function and the double bond in the beta-gamma position! Benzylalcohol was recovered after the reaction.

Scheme 3: Alternative substrates for the 1,4-addition reaction to methyl-hydroxy units.

In a final attempt we tried to use free hydroxy compound 11 directly under ACA-conditions with an excess of methyl Grignard reagent. The first equivalent deprotonates the alcohol leading to the alkoxy magnesium species which should then undergo the ACA. Both with the Josiphos/CuBr system and the tol-BINAP/CuI system only small amounts (~10%) of product 18 were obtained with low/no diastereoselectivity. Formation of the possible epoxide product was not observed.

Because of the difficulties observed in this strategy we decided to focus on alternative routes for the construction of the hydroxy-methyl substructure.

6.3.2 Synthesis of hydroxyphthioceranic acid: second approach

In our second attempt to synthesize hydroxyphthioceranic acid we started with a h-AAA on substrate 19 derived from cinnamic acid bromide and acrolein. Product 20 of the h-AAA was subsequently used under ring closing conditions with 1 mol% Hoveyda-Grubbs second-generation catalyst to provide lactone 21 in high yield (87%). Lactone 21 was treated
with stoichiometric amounts of Gillman reagent (Me₂CuLi) which resulted selectively in trans substituted lactone 22. Lactone 22 was reduced with DIBAL-H to racemic lactol 23 in 98% yield. Olefination reaction of the lactol with a Wittig reagent or a HWE reagent did not lead to desired product 24 and the starting material was recovered. Olefination reactions on related five-membered lactols with different substituents have been reported.¹¹ The substituents on lactol 23 may account for the lack of reactivity in this case.

Scheme 4: Ring closing metathesis and lactol olefination strategy.

Because the lactol was not reactive in the olefination reaction, we decided to open lactone 22 and proceed our synthesis from that point.
6.3.3 Synthesis of hydroxyphthioceranic acid: final approach

Lactone 22 was hydrolysed with exactly one equivalent of KOH in a mixture of THF and H\textsubscript{2}O (Scheme 5). After complete hydrolysis, analyzed by TLC, all the solvents were removed under reduced pressure. The remaining solid was co-evaporated with 5 portions of dry toluene to strip of trace amounts of water. The potassium carboxylate salt was dissolved in dry DMF under nitrogen atmosphere and 5 equivalents of isopropyl bromide were added. \textit{i}-Propylester 25 was obtained this way in 99% yield over these two transformations.

Alcohol 25 was protected with TBDPSOTf in 86% yield. Ester 26 was reduced \textit{in situ} with one equivalent of DIBAL-H to the corresponding aldehyde which was subsequently treated with HWE reagent in one pot to yield unsaturated thioester 27 in 80% yield. Only trace amounts of the \textit{Z}-isomer were observed which could be removed by column chromatography. Asymmetric conjugate addition on substrate 27 with (S,\textit{R})-Josiphos resulted in the expected \textit{syn}-product 28 with complete stereocontrol; the \textit{anti}-product was not visible in the \(^1\)H-NMR spectrum (Figure 2). The \textit{anti}-product was also prepared by switching to (\textit{R},S\textsubscript{\textit{R}})-Josiphos and this resulted in a dr of 6 : 1. As was shown in chapter 2 there is a clear substrate preference for the \textit{syn}-product which cannot be completely suppressed by the catalyst.
Scheme 5: Ring closing metathesis and lactone opening strategy.

Figure 2 shows the $^1$H-NMR of the two diastereomeric products. As was described in chapter 2 for the iterative synthesis of mycocerosic acid and phthioceranic acid the ABX-pattern of the alpha-hydrogen atoms can be used to determine the relative stereochemistry of the products of the reaction.
Figure 2: Partial $^1$H-NMR spectra of syn and anti isomer.

With substrate 28 in hand as a single diastereomer, we performed six additional asymmetric 1,4-additions in an iterative fashion. Reduction of the thioester 28 to the corresponding aldehyde followed by HWE-olefination results in an unsaturated thioester which is used in the ACA. These steps were repeated for thioester 30, 31, 32, 33, 34, till we reached thioester 35 in 25 steps starting from 19 (see Scheme 6). Remarkably all the iterative steps were executed with complete stereocontrol without any formation of the undesired anti-product.
Scheme 6: Iterative ACA steps for the introduction of seven methyl substituents.

Because we were curious to see how the ACA would perform on substrate 36 (Scheme 7) for the formation of anti-product of 37, a small sample was put under ACA conditions with (R,S)-Josiphos. The diastereomeric ratio was clearly visible in $^1$H-NMR by comparison of the syn- and anti-products and was found to be 7 : 1 in favor of the desired anti-product (Figure 3).
Scheme 7: Formation of anti-product 37.

Figure 3: $^1$H-NMR of syn-35 and anti-37 isomers.

After we introduced the nine desired stereocenters with perfect stereocontrol, we had to shorten the molecule by one CH$_2$ moiety to obtain an alpha methyl-branched acid as compared to beta methyl-branched thioester 35. We first transformed thioester 35 into the corresponding methyl ketone 38 (Scheme 8) by treatment with Me$_2$CuLi (Gillman
reagent). Baeyer-Villiger oxidation of ketone 38 selectively gave rise to internally oxidized product 39 (partially hydrolyzed). Simple hydrolysis to alcohol 40 (63%, two steps) followed by oxidation under neutral conditions afforded the acid which was directly treated with trimethylsilyl diazomethane to methyl ester 41. In the final step the TBDP silyl protecting group was removed with TBAF (tetrabutylammonium fluoride) and the methyl ester of hydroxyphthioceranic acid (9) was obtained with an overall yield of 1.6% in 30 steps.

![Scheme 8: Synthetic route to anti-9 involving shortening of ketone 38 via Baeyer-Villiger oxidation.](image)

The optical rotation of methyl ester anti-9, [α] = +16.0° (CHCl₃) was not that different from what has been reported in literature for the natural product, [α] = +23° (CHCl₃). It has to be mentioned that the reported value was obtained from a mixture of homologues of hydroxyphthioceranic acid in which the number of methyl groups varies from 4 to 9. To obtain indisputable evidence of the unknown stereochemistry of the hydroxy group we also synthesized its diastereomer by performing a Mitsunobu reaction on anti-9 which inverses the stereocenter. A small sample of anti-9 was treated with DEAD (diethylazodicarboxylate), PPh₃ and para-nitrobenzoic acid and 42 was obtained. Trans-esterification of 42 with methanol and catalytic amounts of NaCN led to the desired product in 182
85% yield over two steps. The optical rotation which was measured for syn-9 was almost identical to that for anti-9, \([\alpha] = +16.4^\circ\) (CHCl₃) so we had to conclude that the stereochemistry of the hydroxy group could not be established in this way.

Scheme 9: Syn-hydroxy formation by Mitsunobu reaction.

Only a direct comparison with the natural product could give absolute proof. We were kindly provided with a small sample of cell wall extract containing Sulfolipid-I by Dr. Gilleron\(^{12}\) extracted from *Mycobacterium tuberculosis* (isolated as is described by Goren\(^{13,14}\)). Trans-esterification of SL-I with NaCN in MeOH resulted in a mixture of fatty acid methyl esters which was used to compare to both synthetic isomers.
6.3.4 Elucidation of the C17-hydroxy-stereocenter

Mass analysis of the natural sample gave us information about the presence of 9 in the natural sample. The exact mass of synthetic syn-9 and anti-9 (Measured Mass: 605.6260, 605.6255 Da respectively, Calculated Mass: 605.6231 Da, M – H$_2$O) was also found in the natural sample; Measured Mass: 605.6254 and therefore, we were sure that the synthesized analogue is present in the natural sample.

HPLC analysis of the two synthetic diastereomers on an Alltima HP Silica 3µ 100 mm x 2.1 mm Column (Grace Davison Discovery Sciences) with an ELSD (Evaporative Lightscattering Detector) detector and heptane/isopropanol 99.5/0.5 as the mobile phase resulted in a remarkable difference in retention time for the syn-9 and anti-9 stereoisomers, of 4.54 min, 11.56 min, respectively (Figure 4).

Because the natural sample contains all the possible fatty acids from sulfolipid-I we also injected the methyl esters of phthioceracic acid (4.35 min) (Chapter 2) and palmitic acid (5.31 min) for comparison.

The HPLC trace of the esterfied natural product showed a broad series of peaks as was expected because of all the possible homologues of hydroxyphthioceracic acid and phthioceracic, next to palmitic acid. Identifying the signal of synthetic analogue syn-9 (4.35 min) in the natural sample proved to be very difficult because of the many small peaks that can be found close to t = 4.35 min. However, it was clear that synthetic analogue anti-9 (11.56 min) was not present in the natural sample.
The hydrolyzed natural SL-I methyl ester mixture was also compared to both syn-9 and anti-9 by $^1$H- and $^{13}$C-NMR. Although the mixture contains a series of homologues with a different number of methyl branches, the hydroxy-methyl relationship in all of them is expected to be identical. First
we compared the $^1$H-NMR of the mixture to that of both synthetic isomers. We discovered that the chemical shift of the CH-proton signal for the CH next to the hydroxy functionality (Figure 5) differs for both synthetic isomers (3.47 vs 3.50 ppm). Comparison with the mixture of methyl esters obtained from natural sulfolipid-I clearly showed that the natural product is the syn-isomer because the chemical shift of the CH-proton signal matches perfectly with that of syn-9.

Figure 5: $^1$H-NMR of syn-9 and anti-9 compared to the natural product (mixture of analogues).

To obtain additional evidence for the methyl-hydroxy syn-relationship, we compared the chemical shifts in $^{13}$C-NMR and APT. Syn-9 and anti-9 show very characteristic chemical shifts for all carbon atoms positioned closely to the vicinal methyl-hydroxy structural unit (Figure 6). The chemical shifts for anti-9 are 15.84 (q), 32.72 (t), 36.26 (d), 40.10 (t), 75.73 (d) compared to the chemical shifts for the same carbon atoms in syn-9; 14.01 (q), 34.90 (t), 35.08 (d), 41.16 (t), 74.34 (d).
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Figure 6: $^{13}$C-APT spectrum for syn-9 and anti-9 isomers.

$^{13}$C-NMR of the natural product (Figure 7) confirmed what we already concluded from the $^1$H-NMR chemical shifts and HPLC analysis. Chemical shifts match perfectly with the signals of syn-9. We found that the chemical shifts for synthetic versus natural compound are identical within the error margin: (14.01 vs 14.00), (34.90 vs 34.90), (35.08 vs 35.06), (41.16 vs 41.13), (75.34 vs 75.31). The chemical shifts expected for the anti motif could not be found in the natural sample providing additional evidence that natural hydroxyphthioceranic acid possesses a syn-hydroxy group.
6.4 Conclusions

This chapter describes the first total synthesis of hydroxyphthioceranic acid following almost exclusively a catalytic asymmetric route. Asymmetric copper-catalyzed conjugate addition and allylic substitution reactions with Grignard reagents were used as the key steps of the synthesis. All nine stereocenters of hydroxyphthioceranic acid were introduced with perfect stereocontrol and hydroxyphthioceranic acid was obtained in 32 steps as a single diastereomer in 1.4% overall yield.

Both possible stereoisomers of the 17-hydroxy group in hydroxyphthioceranic acid were synthesized and compared to the natural product and the configuration could be elucidated by comparison of the $^1$H-NMR, $^{13}$C-NMR, and APT spectra and HPLC analysis. The absolute configuration of the 17-hydroxy group was established as $R$.

An alternative strategy for the construction of syn-hydroxyphthioceranic acid can now be considered because our initial synthetic strategy was designed for the anti-methyl-hydroxy relationship and not for the natural occurring syn-relationship. In a new strategy the inversion step under Mitsunobu conditions followed by hydrolysis should be avoided. A new route is currently under investigation.
6.5 Acknowledgement

We gratefully acknowledge Dr. Gilleron and co-workers for providing us with a natural sample of SL-I containing cell extract from *M. tuberculosis*. The elucidation of the C17-hydroxy group in hydroxyphthioceric acid would have been impossible without their kind help.

6.6 Experimental

**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 aqueous 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 the product purified by flash chromatography.

**DIBAL-H reduction (procedure B):** 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 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 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.

**Horner-Wadsworth-Emmons olefination (HWE olefination) (procedure C):** To a stirred solution of (EtO)₂POCHCOEt (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 subsequently stirred for 8 h. The reaction mixture was quenched with a saturated aq. solution of NH₄Cl. 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 to afford the desired α,β-unsaturated thioester.

**General remark:** During all the iterative steps we found that it was crucial to put the crude products as a dilute solution on the silica column in the chromatography steps for optimal separation of the products.

**(-)-Benzoic acid-1-vinyl-pentadecanyl ester (4)**

First a solution of pentadecylmagnesium bromide (0.45 M) was prepared in ether. The solution was cooled to –60 ºC and 70 mL CH₂Cl₂ was added directly and the mixture was stirred vigorously. A solution of 1 mol% (–)-(S,S₆)-Taniaphos (34.5 mg) in 2 mL of CH₂Cl₂ was added and the suspension was stirred for 10 min. Substrate 3 (1.000 g, 4.149 mmol) in CH₂Cl₂ (10 mL) was added dropwise over 15 min. The reaction mixture was quenched with 3 mL MeOH after 16 h at –60 ºC. A saturated aq. NH₄Cl solution (50 mL) was added, together with 50 mL ether and the mixture was brought to rt and stirred for 30 min. The layers were separated and the aqueous layer was extracted with 2 additional portions of 100 mL ether. The organic layers were combined, dried on MgSO₄ and concentrated under reduced pressure and purified by flash chromatography (pentane/diethyl ether, 40:1) to afford 4 as a colorless oil (1.307 g, 85% yield). [α]D = –16.4° (c = 1.82, CHCl₃): ¹H NMR (400 MHz) δ 8.07 (d, J = 8.4 Hz, 2 H), 7.58-7.52 (m, 1 H), 7.47-7.41 (m, 2 H), 5.95-5.84 (m, 1 H), 5.49 (q, J = 6.5 Hz, 1 H), 5.32 (dd, J = 0.6, 17.2 Hz, 1 H), 5.20 (dd, J = 1.0, 10.5 Hz, 1 H), 1.87-1.66 (m, 2 H), 1.45-1.20 (m, 26 H), 0.88 (t, J = 6.8 Hz); ¹³C-NMR (CDCl₃, 100.6 MHz) δ 165.91 (s), 136.64 (d), 132.84 (d), 130.67 (s), 129.65 (d, 2 x C), 128.30 (d, 2 x C), 116.51 (t), 75.42 (d), 34.37 (t), 31.94 (t), 29.71 (t, 4 x C), 190
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29.72 (t), 29.66 (t), 29.60 (t), 29.51 (t), 29.44 (t), 29.43 (t), 25.11 (t), 22.73 (t), 14.15 (q). HRMS(El+) calculated for C_{25}H_{40}O_2 372.3028, found 372.3025.

(−)-(R)-Octadec-1-en-3-ol (10)

To a stirred solution of 4 (145 mg, 0.390 mmol) in 2 mL THF and 2 mL EtOH 3 equiv. of LiOH were added and the resulting mixture was stirred for 16 h at rt. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (eluent pentane/ether 9:1) to afford 10 as a white solid (99 mg, 96% yield). [α]_D = −4.6° (c = 1.00, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 5.87 (ddd, J = 6.2, 10.4, 16.7 Hz, 1H), 5.16 (m, 2H), 4.09 (m, 1H), 1.51 (m, 1H), 1.28 (br, 28H), 0.88 (t, J = 6.8 Hz, 3H). ^13C NMR (CDCl_3, 100.6 MHz) δ 141.32 (d), 114.49 (t), 73.28 (d), 37.05 (t), 31.91 (t), 29.68 (t), 29.65 (t), 29.58 (t), 29.55 (t), 29.35 (t), 25.32 (t), 22.68 (t), 14.11 (q). HRMS(ESI−) calculated for C_{18}H_{35}O^− (M−H) 267.2693, found 267.2698.

(−)(R,E)-S-Ethyl 4-hydroxynonadec-2-enethioate (11)

(140 mg, 0.522 mmol) was dissolved in 5 mL dry CH_3Cl and nitrogen was bubbled through for 30 min. S-ethyl acrylate (303 mg, 2.612 mmol) was added via a syringe and 1 mol% of Hoveyda-Grubbs second generation (2.9 mg) was added in one portion and the mixture was stirred for 1 d under a nitrogen atmosphere. The solution was concentrated under reduced pressure and the crude material was purified by flash chromatography (eluent pentane/ether 9:1) to afford 11 as a white wax (110 mg, 60% yield). [α]_D = −16.9° (c = 1.10, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 6.85 (dd, J = 4.8, 15.5 Hz, 1H), 6.31 (dd, J = 1.6, 15.5 Hz, 1H), 4.30 (m, 1H), 2.95 (q, J = 7.4 Hz, 2H), 1.85 (m, 1H), 1.57 (m, 2H), 1.45-1.10 (br, 29H), 0.87 (t, J = 6.8 Hz, 3H). ^13C NMR (CDCl_3, 100.6 MHz) δ 190.16 (s), 145.78 (d), 126.87 (d), 71.04 (d), 36.66 (t), 31.89 (t), 29.66 (t, 3 x C), 29.63 (t, 2 x C), 29.60 (t), 29.54 (t), 29.47 (t), 29.44 (t), 29.33 (t), 25.20 (t), 23.23 (t), 22.66 (t), 14.68...
(q), 14.09 (q). HRMS(ESI−) calculated for C_{21}H_{39}O_{2}S^{−} (M − H) 355.2675, found 355.2673.

(+)-(R,E)-S-Ethyl 4-(t-butyldiphenylsilyloxy)nonadec-2-enethioate (12)

A solution of TBDPSCI (0.161 mL, 0.620 mmol) and AgOTf (175 mg, 0.682 mmol) was stirred in 3 mL CH_{2}Cl_{2} for 1 h under N_{2} atm. Lutidine (1.240 mmol) was added to the solution followed by 11 (110 mg, 0.310 mmol) in 1 mL CH_{2}Cl_{2} at −20 °C (ice bath with NaCl). The temperature of the reaction mixture came to rt overnight; and the mixture was then filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 12 as a colorless oil (150 mg, 81% yield). [α]_{D}^{20} = +33.2° (c = 1.50, CHCl_{3}). ^{1}H-NMR (400 MHz, CDCl_{3}): δ 7.64 (dd, J = 6.5, 23.6 Hz, 4H), 7.39 (m, 6H), 6.77 (dd, J = 5.0, 15.7 Hz, 1H), 6.16 (dd, J = 0.9, 15.5 Hz, 1H), 4.32 (m, 1H), 2.94 (q, J = 7.4 Hz, 2H), 1.45 (m, 2H), 1.38-1.01 (br, 29H), 1.09 (s, 9H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C-NMR (CDCl_{3}, 100.6 MHz) δ 190.14 (s), 145.97 (d), 135.82 (d, 4 x C), 133.88 (s, 2 x C), 129.74 (d, 2 x C), 127.58 (d, 4 x C), 127.19 (d), 72.46 (d), 36.84 (t), 31.91 (t), 29.69 (t, 2 x C), 29.65 (t, 2 x C), 29.60 (t), 29.51 (t), 29.44 (t), 29.37 (t), 29.35 (t), 27.01 (t) (q, 3 x C), 24.06 (t), 23.14 (t), 22.68 (t), 19.34 (s), 14.72 (q), 14.11 (q). HRMS(ESI+) calculated for C_{37}H_{56}O_{2}SSi (M + Na^+) 617.3814, found 617.3824.

(+)-(R,E)-S-Ethyl 4-(benzyloxy)nonadec-2-enethioate (16)

To a stirred solution of 10 (517 mg, 1.929 mmol) in THF (10 mL) under nitrogen atmosphere, NaH (60% in oil, 3.171 mmol) was added at 0 °C. After stirring for 30 min, benzyl bromide (0.377 mL, 3.153 mmol) was added together with a catalytic amount of Bu_{4}NI (5 mg). The reaction mixture was stirred for 24 h at rt, quenched with a saturated aq. solution of NH_{4}Cl and ether was added (20 mL). The layers were separated and the water layer was extracted with 2 additional portions of 20 mL ether. The organic layers
were combined and dried on MgSO\textsubscript{4} and concentrated under reduced pressure. The crude product was flushed over a small plug of silica with diethyl ether as the eluent. After evaporation of the diethylether the crude product 15 was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) and 5 equiv. of S-ethyl acrylate (1.118 g, 9.645 mmol) were added via a syringe and 1 mol% of Hoveyda-Grubbs second generation (12 mg) was added in one portion. The mixture was stirred for 1 d under a nitrogen atmosphere at rt. The solution was concentrated under reduced pressure and crude 16 was purified by flash chromatography (eluent pentane/ether 40:1) to afford 16 as a colorless oil (516 mg, 60% yield over 2 steps). [α]\textsubscript{D} = +20.2° (c = 1.00, CHCl\textsubscript{3}). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): 7.31 (m, 5H), 6.79 (dd, \(J = 6.3, 15.6\) Hz, 1H), 6.29 (dd, \(J = 1.2, 15.6\) Hz, 1H), 4.49 (dd, \(J = 11.8, 84.1\) Hz, 1H), 3.94 (m, 1H), 2.98 (q, \(J = 7.4\) Hz, 2H), 1.61 (m, 2H), 1.31 (t, \(J = 7.4\) Hz, 3H), 1.26 (br, 27H), 0.89 (t, \(J = 6.8\) Hz, 3H). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}, 100.6 MHz) \(\delta\) 189.82 (s), 144.24 (d), 138.07 (s), 128.66 (d), 128.35 (d), 127.67 (d), 127.62 (d), 77.99 (d), 71.03 (t), 34.92 (t), 31.89 (t), 29.67 (t, 4 x C), 29.63 (t, 3 x C), 29.60 (t), 29.55 (t), 29.46 (t), 29.45 (t), 29.33 (t), 25.11 (t), 23.20 (t), 22.66 (t), 14.69 (q), 14.08 (q). HRMS(ESI+) calculated for C\textsubscript{28}H\textsubscript{46}O\textsubscript{2}S (M + Na\textsuperscript{+}) 469.3116, found 469.3106.

(+)-(15S)-1-Vinyl-pentadecanyl-(2E)-3-phenylacrylate (20)

First a solution of pentadecylmagnesium bromide (0.45 M) was prepared in ether. The solution was cooled to –60 °C and 120 mL CH\textsubscript{2}Cl\textsubscript{2} was added directly and the mixture was stirred vigorously. A solution of 1.1 mol% (+)-(R,R)-Taniaphos (142 mg) and 1.0 mol% (38.5 mg) CuBr•SMe\textsubscript{2} in 5 mL CH\textsubscript{2}Cl\textsubscript{2} was added and the suspension was stirred for 10 min. Substrate 19 (5.000 g, 18,727 mmol) was added dropwise in CH\textsubscript{2}Cl\textsubscript{2} (2 portions of 10 mL) over 1 h. The reaction mixture was quenched with 5 mL MeOH after 16 h at –60 °C. A saturated aq. NH\textsubscript{4}Cl solution (80 mL) was added together with 200 mL ether and the mixture was brought to rt and stirred for 30 min. The layers were separated and the aqueous layer was extracted with 2 additional portions of 200 mL ether. The organic layers were combined and dried on MgSO\textsubscript{4} and concentrated under reduced pressure and the product purified by flash chromatography (eluent pentane/ether 40:1) to
afford 20 as a colorless oil (5.683 g, 76% yield). \([\alpha]_D = +12.6^\circ\) (c = 1.03, CHCl\(_3\)). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.70 (d, \(J = 16\) Hz, 1H), 7.53 (m, 2H), 7.37 (m, 3H), 6.46 (d, \(J = 16\) Hz, 1H), 5.85 (m, 1H), 5.37 (apparent q, \(J = 8\) Hz, 1H), 5.29 (td, \(J = 1.3\), 17.3 Hz, 1H), 5.18 (td, \(J = 1.1\), 10.5 Hz, 1H), 1.74-1.61 (m, 2H), 1.48-1.08 (m, 26H), 0.88 (t, \(J = 6.8\) Hz, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100.6 MHz) \(\delta\) 166.32 (s), 144.61 (d), 136.70 (d), 134.36 (s), 130.23 (d), 128.82 (d, 2 x C), 128.01 (d, 2 x C), 118.39 (d), 116.49 (t), 74.91 (d), 34.33 (t), 31.92 (t), 29.73 (t), 29.63-29.58 (t, 6 x C), 29.49 (t), 29.40 (t), 29.31 (t), 25.09 (t), 22.74 (t), 14.06 (q), HRMS(EI+) calculated for \(\text{C}_{27}\text{H}_{42}\text{O}_2\) 398.3185, found 398.3180.

(+)-(5S)-5-Pentadecylfuran-2(5H)-one (21)

- A solution of 2.435 g 20 (6.118 mmol) in 25 mL CH\(_2\)Cl\(_2\) was stirred at room temperature and nitrogen was bubbled through the solution for 15 min. Hoveyda-Grubbs second generation, 38 mg (1 mol%), was added in one portion and the solution was refluxed for 24 h under a nitrogen atmosphere. After 24 h the reaction mixture was cooled down to room temperature and the solvents were removed under reduced pressure. Crude 21 was purified by flash chromatography (eluent pentane/ether 1:1) to afford 21 as a white wax (1.578 g, 87% yield). \([\alpha]_D = +50.0^\circ\) (c = 1.04, CHCl\(_3\)). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.43 (dd, \(J = 1.5\), 5.7 Hz, 1H), 6.09 (dd, \(J = 2.0\), 5.7 Hz, 1H), 5.02 (m, 1H), 1.79-1.59 (m, 2H), 1.47-1.37 (m, 2H), 1.35-1.10 (m, 24H), 0.86 (t, \(J = 6.7\) Hz, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100.6 MHz) \(\delta\) 173.80 (s), 156.32 (d), 121.51 (d), 83.42 (d), 33.37 (d), 31.91 (d), 29.57 (d, 4 x C), 29.60 (d), 29.55 (d), 29.51 (d), 29.33 (d), 29.25 (d), 29.35 (d), 24.90 (d), 22.71 (d), 14.06 (q), HRMS(EI+) calculated for \(\text{C}_{19}\text{H}_{34}\text{O}_2\) 294.2559, found 294.2544.

(–)-(4R,5S)-4-Methyl-5-pentadecylidihydrofuran-2(3H)-one (22)

- To a stirred solution of CuI (3.414 g, 17.925 mmol) in 80 mL ether at –20 \(^\circ\)C (ice bath with NaCl), MeLi (21.286 ml 1.6M in ether, 34.058 mmol) was carefully added over 10
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min. After 15 min of stirring, a solution of substrate 21 (1.050 g, 3.585 mmol) in 15 mL ether was added and stirring was continued for 2 h at –20 °C. The reaction mixture was quenched with 50 mL saturated aq. NH₄Cl solution and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with 3 portions of 100 mL ether. The combined organic fractions were dried on MgSO₄ and concentrated under reduced pressure. Crude 22 was purified by flash chromatography (eluent pentane/ether 1:1) to afford 22 as a white solid (1.045 g, 94%). [α]D = –40.4° (c = 1.00, CHCl₃).

1H-NMR (400 MHz, CDCl₃): δ 4.00 (m, 1H), 2.71-2.62 (m, 1H), 2.28-2.10 (m, 2H), 1.69-1.14 (br m, 28H), 1.13 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 6.4 Hz, 3H);

13C-NMR (CDCl₃, 100.6 MHz) δ 176.43 (s), 87.34 (d), 37.00 (d), 36.02 (t), 33.89 (t), 31.76 (t), 29.62-29.51 (6 x C, t), 29.42 (t), 29.28 (t), 29.31 (t), 29.33 (t), 25.55 (t), 22.62 (t), 17.28 (q), 14.01 (q). HRMS(EI+) calculated for C₂₀H₃₈O₂ 310.2872, found 310.2888.

(4R,5S)-4-Methyl-5-pentadecyltetrahydrofuran-2-ol (23)

To a stirred solution of lactone 22 (191 mg, 0.616 mmol) in 20 ml CH₂Cl₂ at –70 °C 1.1 equivalent (0.678 mmol) of DIBAL-H (1M in CH₂Cl₂) was added. The temperature was brought to –30 °C over 2 h. A saturated Rochelle salt solution (15 ml) was added to quench the reaction. The organic layer was separated and the water layer was extracted with three portions of 15 ml CH₂Cl₂. The combined organic layers were dried on MgSO₄ and the solvent evaporated under reduced pressure. The crude lactol was purified by flash chromatography (eluent pentane/ether 1:1) to afford 23 as a mixture of diastereomers (189 mg, 98%). 1H-NMR (400 MHz, CDCl₃): δ 5.49 (m, 0.5H), 5.41 (m, 0.5H), 3.77 (d, J = 3.1 Hz, 0.5H), 3.68 (m, 0.5H), 3.50 (d, J = 3.1 Hz, 0.5H), 3.46 (m, 0.5H), 2.34 (m, 0.5H), 2.12 (m, 0.5H), 2.04 (m, 0.5H), 1.77 (m, 9H), 1.48-1.22 (br, 18H), 1.04 (d, J = 6.7 Hz, 1.5H), 1.01 (d, J = 6.4 Hz, 1.5H), 0.86 (t, J = 6.8 Hz, 3H);

13C-NMR (CDCl₃, 100.6 MHz) δ (97.84, 97.60) (d), (87.11, 84.40) (d), (42.49, 42.25) (t), (38.67, 36.44) (d), 35.74 (t), 33.83 (t), 31.90 (t), 29.78 (t), 29.76 (t), 29.68 (t), 29.62 (t), 29.58 (t), 29.55 (t), 29.34 (t), 26.35 (t), 26.27 (t), 22.66 (t), (17.08, 16.76) (q), 14.09 (q). HRMS(ESI–) calculated for C₂₀H₃₈O₂ (M – H) 311.2956, found 311.2953.
(-)-(3R,4S)-iso-Propyl 4-hydroxy-3-methylnonadecanoate (25)

Lactone 22 (436 mg, 1.406 mmol) was dissolved in a mixture of 1:1 THF/H₂O (10 mL) and 89.8 mg KOH (1.406 mmol) was added. The mixture was heated to 60 °C for 16 h and then cooled down to rt. The solvents were removed under reduced pressure (caution, soap formation). The crude potassium salt was stripped with 3 portions (5 mL) of dry toluene to remove the final traces of water. The crude material was dissolved in dry DMF (30 mL) under a N₂ atm. and 5 eq. of isopropyl bromide (0.660 mL, 7.030 mmol) were added. This mixture was stirred for 2 d at rt. Ether (100 mL) and H₂O (100 mL) were added and the organic layer was separated from the water phase after vigorous shaking. The organic layer was washed with one portion of ether (50 mL). The combined organic layers were washed with brine (100 mL) and subsequently dried on MgSO₄ and evaporated under reduced pressure. The crude ester was purified by flash chromatography (eluent pentane/ether 9:1) to afford 25 as a white solid (496 mg, 99%). [α]₀ = −7.5° (c = 1.10, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 4.99 (heptet, J = 6.4 Hz, 1H), 3.36 (m, 1H), 2.45 (dd, J = 5.4, 15.0 Hz, 1H), 2.16 (dd, J = 7.7, 15.0 Hz, 1H), 2.04-1.95 (m, 1H), 1.87 (d, J = 5.8 Hz, 1H), 1.52-1.11 (br, 28 H), 1.22 (d, J = 6.3 Hz, 6H), 0.94 (d, J = 6.9 Hz, 3H); ¹³C-NMR (CDCl₃, 100.6 MHz) δ 173.42 (s), 75.54 (d), 67.57 (d), 37.82 (t), 36.21 (d), 34.46 (t), 31.88 (t), 29.65-29.59 (9 x C, t), 29.32 (t), 25.77 (t), 22.65 (t), 21.80 (q), 21.76 (q), 16.63 (q), 14.08 (q). MS(Cl⁺) for C₂₃H₄₆O₃: m/z(%) = 328 (100%, M – isopropyl), 388 (6.6%, M + NH₄⁺). HRMS(ESI⁺) calculated for C₂₃H₄₆O₃ (M + Na⁺) 393.3345, found 393.3335.

(+)-(3R,4S)-iso-Propyl 4-(t-butylidiphenylsilyloxy)-3-methylnonadecanoate (26)

A solution of TBDPSCI (0.484 mL, 1.860 mmol) and AgOTf (525.7 mg, 2.046 mmol) was stirred in 5 mL CH₂Cl₂ for 1 h under N₂ atm. Lutidine (3.720 mmol) was added to the solution followed by iso-propyl ester 25 (330 mg, 0.930 mmol) in 1 mL CH₂Cl₂ at -20 °C (ice bath with NaCl). The temperature of 196
the reaction mixture came to rt overnight and the mixture was then filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 26 as a colorless oil (487 mg, 86%). [α]_D = +16.5° (c = 1.15, CHCl₃). 1H-NMR (400 MHz, CDCl₃): δ 6.35 (dd, J = 1.3, 7.7 Hz, 4H), 7.44-7.34 (m, 6H), 6.26 (heptet, J = 6.3 Hz, 1H), 3.58 (m, 1H), 2.44 (dd, J = 3.9, 14.3 Hz, 1H), 2.15 (m, 1H), 2.07 (dd, J = 9.8, 14.3, 1H), 1.38-1.10 (br, 25H), 1.22 (d, J = 6.3 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H), 1.07 (s, 9H), 0.97 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H); 13C-NMR (CDCl₃, 100.6 MHz) δ 173.12 (s), (136.00, 135.94) (d, 4 x C), (134.67, 133.98) (s, 2 x C), (129.48, 129.34) (d, 4 x C), (127.42, 127.29) (d, 2 x C), 76.90 (d), 67.29 (d), 37.08 (t), 34.82 (d), 33.54 (t), 31.91 (t), 29.69-29.36 (7 x C, t), 27.12 (q, 3 x C), 25.29 (t), 22.68 (t), (21.86, 21.77) (q, 2 x C), 19.56 (s), 16.40 (q), 14.11 (q). HRMS(El+) calculated for C_{33}H_{35}O_5Si (M – t-butyl) 551.3921, found 551.3944.

(-)-(5R,6S,E)-S-Ethyl 6-(t-butyldiphenylsilyloxy)-5-methylhex-2-enethioate (27)

![Chemical Structure]

a stirred mixture of iso-propyl ester 26 (0.294 mmol) in CH₂Cl₂ (4 mL) was added DIBAL-H (0.309 mmol, solution in CH₂Cl₂) at -60 °C under nitrogen. Stirring was continued until the reduction was completed (3-5 h). Solution B; To a stirred solution of (EtO)₂POCHCOEt (0.588 mmol) in THF (10 mL) at 0 °C under nitrogen was added n-BuLi (0.441 mmol, solution in hexane). The reaction mixture was stirred for an additional 20 min. Solution B was added dropwise to solution A and after addition the reaction mixture was slowly warmed to rt and stirred for 8 h. The reaction mixture was quenched with a saturated solution of NH₄Cl. 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 (eluent pentane/ether 40:1) to afford α,β-unsaturated thioester 27 as a colorless oil (159 mg, 85%). [α]_D = -3.9° (c = 0.97, CHCl₃). 1H-NMR (400 MHz, CDCl₃): δ 7.68 (d, J = 6.4 Hz, 4H) 7.41 (m, 6H) 6.76 (td, J = 7.4, 15.1 Hz, 1H) 6.03 (d, J = 15.4 Hz, 1H) 3.57 (m, 1H), 2.95 (q, J = 7.4 Hz, 2H) 2.27 (m, 1H) 1.96 (m, 1H) 1.76 (m, 1H), 1.50-1.00 (br, 31H), 1.06 (s, 9H), 0.91 (d, J
HRMS(EI+) calculated for 189.82 (s), 144.51 (d), 135.96 (d, 4 × C), (134.52, 134.07) (s, 2 × C), (129.57, 129.53) (d, 4 × C), 129.41 (d), (127.45, 127.33) (d, 2 × C), 76.86 (d), 37.30 (d), 34.92 (t), 33.00 (t), 31.91 (t), 29.70 (t, 3 × C), 29.66 (t), 29.61 (t), 29.53 (t), 29.51 (t), 29.46 (t), 29.36 (t), 27.12 (q, 3 × C), 25.35 (t), 22.99 (t), 22.68 (t), 22.33 (t), 19.54 (s), 15.58 (q), 14.82 (q), 14.11 (q), 14.05 (q).

HRMS(EI+) calculated for C₃₈H₅₅O₃SSi (M − t-butyl) 595.4005, found 595.4017.

(±)-(3S,5R,6S)-S-Ethyl 6-(t-butyldiphenylsilyloxy)-3,5-dimethylhexanethioate (28)

The title compound was prepared from 27 following procedure A. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 28 as a colorless oil (440 mg, 91%). [α]D = +8.3° (c = 1.27, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 7.68 (m, 4H), 7.40 (m, 6H), 3.57 (m, 1H), 2.85 (q, J = 7.3 Hz, 2H), 2.30 (dd, J = 5.1, 14.5 Hz, 1H), 2.06 (dd, J = 8.8, 14.4 Hz, 1H), 1.87 (m, 1H), 1.56 (m, 1H), 1.40-0.90 (br, 42H), 0.89 (t, J = 6.7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H); ¹³C-NMR (CDCl₃, 100.6 MHz) δ 199.03 (s), (135.94, 135.92) (d, 4 × C), (134.71, 134.39) (s, 2 × C), (129.36, 129.24) (d, 4 × C), (127.31, 127.21) (d, 2 × C), 76.98 (d), 50.54 (t), 39.80 (t), 35.31 (d), 31.99 (t), 31.84 (t), 29.62 (t, 6 × C), 29.58 (t), 29.48 (t), 29.44 (t), 29.28 (t), 28.54 (d), 27.07 (q, 3 × C), 26.07 (t), 23.13 (t), 22.60 (t), 20.45 (q), 19.47 (s), 14.83 (q), 14.72 (q), 14.04 (q). HRMS(EI+) calculated for C₃₈H₅₅O₃SSi (M − t-butyl) 595.4005, found 595.4017.

(±)-(5R,7R,8S,E)-S-Ethyl 8-(t-butyldiphenylsilyloxy)-5,7-dimethyltricos-2-enethioate (28b)

The title compound was prepared from 28 following procedure B and C. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 28b as a colorless oil (1.623 g, 90%). [α]D = +4.8° (c = 1.32, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 7.68 (m, 4H), 7.40 (m, 6H), 6.75 (dt, J = 8.0, 15.2 Hz, 1H),
5.99 (dt, J = 1.4, 15.5 Hz, 1H), 3.55 (m, 1H), 2.95 (q, J = 7.4 Hz, 2H), 2.00 (m, 1H), 1.72 (m, 1H), 1.61 (m, 1H), 1.49-1.00 (br, 3H), 1.07 (s, 9H), 0.89 (t, J = 6.4 Hz, 3H), 0.89 (d, J = 6.1 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H); $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) δ 189.82 (d), 143.94 (d), (135.99, 135.96) (d, 4 x C), (134.67, 134.45) (s, 2 x C), 129.74 (d), (129.39, 129.29) (d, 2 x C), (127.33, 127.25) (d, 4 x C), 76.95 (d), 39.82 (t), 38.55 (t), 35.43 (d), 31.88 (t), 29.89 (d), 29.65 (t, 7 x C), 29.62 (t), 29.52 (t), 29.48 (t), 29.32 (t), 27.10 (q, 3 x C), 26.18 (t), 22.96 (t), 22.65 (t), 20.46 (q), 19.49 (s), 14.80 (q), 14.78 (q), 14.09 (q). HRMS(EI+) calculated for C$_{39}$H$_{61}$O$_2$SSi (M – t-butyl) 621.4162, found 621.4191.

(+)-(3S,5R,7R,8S)-Ethyl 8-(t-butyldiphenylsilyloxy)-3,5,7-trimethyltricosanethioate (30)

The title compound was prepared from 28b following procedure A. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 30 as a colorless oil (499 mg, 95%). [α]$_D$ = +7.5° (c = 1.34, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.70 (m, 4H), 7.39 (m, 4H), 3.57 (m, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.45 (dd, J = 4.8, 14.3 Hz, 1H), 2.14 (dd, J = 8.8, 14.3 Hz, 1H), 2.02 (m, 1H), 1.64 (m, 1H), 1.50-1.00 (br, 29H), 1.08 (s, 9H), 0.90 (t, J = 7.6 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.71 (d, J = 6.4 Hz, 3H); $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) δ 199.17 (s), (136.04, 136.01) (d, 4 x C), (134.79, 134.57) (s, 2 x C), (129.39, 129.29) (d, 2 x C), (127.33, 127.26) (d, 4 x C), 76.79 (d), 50.73 (t), 44.25 (t), 40.68 (t), 35.54 (d), 31.92 (t), 31.64 (t), 29.71 (t, 6 x C), 29.66 (t), 29.57 (t), 29.55 (t), 29.37 (t), 28.50 (d), 27.51 (d), 27.14 (q, 3 x C), 26.35 (t), 23.23 (t), 22.69 (t), 20.75 (q), 20.46 (q), 19.52 (s), 14.97 (q), 14.82 (q), 14.13 (q). HRMS(EI+) calculated for C$_{39}$H$_{61}$O$_2$SSi (M – t-butyl) 637.4475, found 637.4440.


The title compound was prepared from 30 following procedure B and C. The crude material was
purified by flash chromatography (eluent pentane/ether 40:1) to afford 30b as a colorless oil (1.235 g, 71%). \([\alpha]_D = +4.8^\circ (c = 1.32, \text{CHCl}_3)\). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 7.68 (m, 4H), 7.38 (m, 6H), 6.82 (dt, J = 8.0, 15.2 Hz, 1H), 6.07 (dt, J = 1.4, 15.5 Hz, 1H), 3.56 (m, 1H), 2.95 \(q, J = 7.4\) Hz, 2H), 2.14 (m, 1H), 1.82 (m, 1H), 1.64 (m, 2H), 1.50-1.00 (br, 36H), 1.07 (s, 9H), 0.89 (t, \(J = 7.0\) Hz, 3H), 0.88 (d, \(J = 7.1\) Hz, 3H), 0.80 (d, \(J = 6.6\) Hz, 3H), 0.70 (d, \(J = 6.5\) Hz, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100.6 MHz) \(\delta 189.89 (s), 144.10 (d), (136.05, 136.01) (d, 4 x C), (134.82, 134.57) (s, 2 x C), 129.80 (d), (129.37, 129.28) (d, 2 x C), (127.32, 127.25) (d, 4 x C), 76.84 (d), 44.29 (t), 40.72 (t), 38.91 (t), 35.58 (d), 31.91 (t), 31.71 (t), 29.84 (d), 29.70 (t, 7 x C), 29.66 (t), 29.57 (t), 29.53 (t), 29.36 (t), 27.15 (q, 3 x C), 26.32 (t), 23.00 (t), 22.68 (t), 20.89 (q), 20.40 (q), 19.52 (s), 15.04 (q), 14.80 (q), 14.11 (q). HRMS(El+) calculated for C\(_{43}\)H\(_{65}\)O\(_2\)SSi (M – t-butyl) 663.4631, found 663.4597.

\((+)-35,55,7R,9R,10S\)-Ethyl 10-(t-butyldiphenylsilyloxy)-3,5,7,9-tetramethylpentacosanethioate (31)

TBDPSO

\(\text{C}_{34}\text{H}_{55}\text{OSS} \)  

The title compound was prepared from 30b following procedure A. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 31 as a colorless oil (1.111 g, 88%). \([\alpha]_D = +8.7^\circ (c = 1.36, \text{CHCl}_3)\). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 7.69 (dd, 1H, J = 1.2, 7.7\) Hz, 4H), 7.38 (m, 6H), 3.58 (m, 1H), 2.88 \(q, J = 7.4\) Hz, 2H), 2.53 \(dd, J = 4.9, 14.3\) Hz, 1H), 2.24 \(dd, J = 8.8, 14.3\) Hz, 1H), 2.09 (m, 1H), 1.67 (m, 1H), 1.50-1.00 (br, 39H), 1.08 (s, 9H), 0.92 (d, \(J = 6.5\) Hz, 3H) 0.90 (t, \(J = 7.6\) Hz, 3H), 0.90 (d, \(J = 6.8\) Hz, 3H), 0.78 (d, \(J = 6.5\) Hz, 3H), 0.68 (d, \(J = 6.4\) Hz, 3H); \(^{13}\)C-NMR (CDCl\(_3\), 100.6 MHz) \(\delta 199.21 (s), (136.05, 136.01) (d, 4 x C), (134.85, 134.55) (s, 2 x C), (129.36, 129.26) (d, 2 x C), (127.32, 127.24) (d, 4 x C), 76.66 (d), 50.88 (t), 45.01 (t), 44.28 (t), 40.61 (t), 35.64 (d), 31.92 (t), 31.65 (t), 29.71 (t, 7 x C), 29.66 (t), 29.56 (t), 29.54 (t), 29.37 (t), 28.59 (d), 27.45 (d), 27.39 (d), 27.16 (q, 3 x C), 26.36 (t), 22.69 (t), 20.74 (q, 2 x C), 20.53 (q), 19.53 (s), 15.19 (q), 14.82 (q), 14.14 (q). HRMS(El+) calculated for C\(_{43}\)H\(_{71}\)O\(_2\)SSi (M – t-butyl) 679.4944, found 679.4971.

The title compound was prepared from 31 following procedure B and C. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 31b as a colorless oil (862 mg, 75%). [α]D = +8.2° (c = 2.03, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.69 (dd, J = 1.5, 7.9 Hz, 4H), 7.38 (m, 6H), 6.87 (dt, J = 8.0, 15.2 Hz, 1H), 6.10 (dt, J = 1.3, 15.4 Hz, 1H), 3.58 (m, 1H), 2.95 (q, J = 7.4 Hz, 2H), 2.21 (m, 1H), 1.92 (m, 1H), 1.67 (m, 2H), 1.50-1.00 (br, 39H), 1.08 (s, 9H). 0.92-0.86 (m, 9H), 0.77 (d, J = 6.5 Hz, 3H), 0.69 (d, J = 6.5 Hz, 3H); 13C-NMR (CDCl3, 100.6 MHz) δ 189.87 (s), 144.07 (d), 136.05, 136.01 (d, 4 x C), 134.86, 134.56 (s, 2 x C), 129.85 (d), 129.35, 129.26 (d, 2 x C), 127.31, 127.24 (d, 4 x C), 76.73 (d), 45.08 (t), 44.30 (t), 40.61 (t), 38.98 (t), 35.65 (d), 31.92 (t), 31.87 (t), 29.89 (d), 29.83 (t, 3 x C), 29.80 (t), 29.71 (t), 29.67 (t), 29.57 (t), 29.54 (t), 29.49 (t), 29.37 (t), 27.52 (d), 27.41 (d), 27.15 (q, 3 x C), 26.32 (t), 23.00 (t), 22.69 (t), 21.20 (q), 20.82 (q), 20.51 (q), 19.53 (s), 15.19 (q), 14.81 (q), 14.12 (q). HRMS(El+) calculated for C43H73O2Si (M – t-butyl) 705.5101, found 705.5079.


The title compound was prepared from 31b following procedure A. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 32 as a colorless oil (761 mg, 86%). [α]D = +8.7° (c = 1.57, CHCl3). 1H-NMR (400 MHz, CDCl3): δ 7.68 (dd, J = 1.3, 7.8 Hz, 4H), 7.38 (m, 6H), 3.58 (m, 1H), 2.88 (q, J = 7.4 Hz, 2H), 2.55 (dd, J = 5.0, 14.3 Hz, 1H), 2.25 (dd, J = 8.8, 14.3 Hz, 1H), 2.12 (m, 1H), 1.68 (m, 1H), 1.56-1.00 (br, 42H), 1.07 (s, 9H), 0.89 (s, J = 6.7 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H), 0.68 (d, J = 6.4 Hz, 3H); 13C-NMR (CDCl3, 100.6 MHz) δ 199.27 (s), 136.05, 136.01 (d, 4 x
C), (134.88, 134.54) (s, 2 × C), (129.35, 129.25) (d, 2 × C), (127.32, 127.24) (d, 4 × C), 76.63 (d), 50.91 (t), 45.04 (t), 45.01 (t), 44.40 (t), 40.55 (t), 35.65 (d), 31.92 (t), 31.64 (t), 29.71 (t, 6 × C), 29.66 (t), 29.57 (t), 29.54 (t), 29.37 (t), 28.63 (d), 27.55 (d), 27.40 (d), 27.28 (d), 27.15 (q, 3 × C), 26.35 (t), 23.25 (t), 22.69 (t), 21.25 (q), 21.15 (q), 20.79 (q), 20.55 (q), 19.53 (s), 15.27 (q), 14.82 (q), 14.13 (q). HRMS(El+) calculated for C_{46}H_{77}O_{2}SSi (M − t-butyl) 721.5414, found 721.5385.


\[ \text{TBDPSO} \]

\[ \text{C}_{46}H_{77}O_{2}SSi \]

The title compound was prepared from 32 following procedure B and C. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 32b as a colorless oil (689 mg, 88%). \([\alpha]_D = +9.1^\circ \) (c = 1.34, CHCl₃). 1H-NMR (400 MHz, CDCl₃): \( \delta \) 7.69 (dd \( J = 1.3, 6.5 \) Hz, 4H), 7.38 (m, 6H), 6.88 (dt, \( J = 1.4, 15.3 \) Hz, 1H), 6.11 (d, \( J = 15.4 \) Hz, 1H), 3.58 (m, 1H), 2.95 (q, \( J = 7.4 \) Hz, 2H), 2.24 (m, 1H), 1.94 (m, 1H), 1.71 (m, 2H), 1.55-0.95 (br, 42H), 1.07 (s, 9H), 0.90 (br, 9H), 0.84 (d, \( J = 6.5 \) Hz, 3H), 0.75 (d, \( J = 6.4 \) Hz, 3H), 0.68 (d, \( J = 6.2 \) Hz, 3H); 13C-NMR (CDCl₃, 100.6 MHz) \( \delta \) 189.91 (s), 144.12 (d), (136.05, 136.02) (d, 4 × C), (134.89, 134.55) (s, 2 × C), 129.85 (d), (129.36, 129.26) (d, 2 × C), (127.32, 127.24) (d, 4 × C), 76.67 (d), 45.09 (t), 45.05 (t), 44.41 (t), 40.60 (t), 39.00 (t), 35.65 (d), 31.93 (t), 31.68 (t), 29.93 (d), 29.71 (t, 8 × C), 29.67 (t), 29.57 (t), 29.55 (t), 29.37 (t), 27.59 (d), 27.42 (d), 27.35 (d), 27.16 (q, 3 × C), 26.35 (t), 23.00 (t), 22.69 (t), 21.25 (q), 21.23 (q), 20.87 (q), 20.54 (q), 19.54 (s), 15.27 (q), 14.82 (q), 14.13 (q). MS(El+) for C_{46}H_{77}O_{2}SSi : m/z(%) = 747 (100%, M − t-Butyl), MS(Cl+) for C_{46}H_{77}O_{2}SSi : m/z(%) = 822 (100%, M + NH₄). HRMS(ESI+) calculated for C_{46}H_{77}O_{2}SSi (M + Na⁺) 827.6167, found 827.6167.


\[ \text{TBDPSO} \]

\[ \text{C}_{46}H_{77}O_{2}SSi \]

The title compound was prepared from 32b following procedure A. The crude material was
purified by flash chromatography (eluent pentane/ether 40:1) to afford 33 as a colorless oil (643 mg, 92%). \([\alpha]_D^0 = +7.9^\circ \ (c = 1.20, \text{CHCl}_3)\). \(^1\text{H}-\text{NMR} (400 \text{ MHz, CDCl}_3)\): \(\delta 7.68 \ (dd, \ J = 1.4, 7.9 \text{ Hz, 4H}), 7.37 \ (m, 6H), 3.57 \ (m, 1H), 2.88 \ (q, \ J = 7.4 \text{ Hz, 2H}), 2.56 \ (dd, \ J = 5.0, 14.3 \text{ Hz, 1H}), 2.26 \ (dd, \ J = 8.8, 14.3 \text{ Hz, 1H})\) 2.12 (m, 1H), 1.68 (m, 1H), 1.56-0.90 (br, 45H), 1.06 (s, 9H), 0.94 (d, \ J = 6.5 \text{ Hz, 3H}), 0.89 (t, \ J = 6.6 \text{ Hz, 3H}), 0.89 (d, \ J = 6.8 \text{ Hz, 3H}), 0.86 (d, \ J = 6.7 \text{ Hz, 3H}), 0.82 (d, \ J = 6.5 \text{ Hz, 3H}), 0.74 (d, \ J = 6.5 \text{ Hz, 3H}), 0.68 (d, \ J = 6.4 \text{ Hz, 3H}). \(^{13}\text{C}-\text{NMR} (\text{CDCl}_3, 100.6 \text{ MHz})\) \(\delta 199.26 \ (s), (136.05, 136.01) \ (d, 4 \times C), (134.89, 134.55) \ (s, 2 \times C), (129.34, 129.24) \ (d, 2 \times C), (127.31, 127.23) \ (d 4 \times C), 76.66 \ (d), 50.91 \ (t), 45.15 \ (t), 45.08 \ (t), 44.40 \ (t), 40.53 \ (t), 35.66 \ (d), 31.91 \ (t), 31.66 \ (t), 29.70 \ (7 \times C), 29.65 \ (t), 29.55 \ (t), 29.53 \ (t), 29.35 \ (t), 28.65 \ (d), 27.63 \ (d), 27.47 \ (d), 27.43 \ (d), 27.34 \ (d), 27.15 \ (q, 3 \times C), 26.35 \ (t), 23.25 \ (t), 22.68 \ (t), 21.30 \ (q), 21.23 \ (q), 21.20 \ (q), 20.80 \ (q), 20.55 \ (q), 19.53 \ (s), 15.29 \ (q), 14.80 \ (q), 14.11 \ (q). \ \text{MS(ESI+)} \text{ for } C_{49}H_{83}O_{2}SSii : m/z(%) = 763 \ (100\%, M + t\text{-butyl}), \text{ MS(ESI+)} \text{ for } C_{51}H_{92}O_{2}SSi : m/z(%) = 838 \ (100\%, M + NH}_4). \ \text{HRMS(ESI+)} \text{ calculated for } C_{51}H_{92}O_{2}SSi (M + Na') 843.6485 found 843.6471.


\[\begin{align*}
\text{TBDPSO} & \quad \text{The title compound was prepared from 33 following procedure B and C. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 33b as a colorless oil (521 mg, 79%). \([\alpha]_D^0 = +8.4^\circ \ (c = 1.88, \text{CHCl}_3)\). \(^1\text{H}-\text{NMR} (400 \text{ MHz, CDCl}_3)\): \(\delta 7.69 \ (dd, \ J = 1.4, 7.9 \text{ Hz, 4H}), 7.38 \ (m, 6H), 6.89 \ (m, 1H), 6.09 \ (dt, \ J = 1.4, 15.5 \text{ Hz, 1H}), 3.59 \ (m, 1H), 2.95 \ (q, \ J = 7.4 \text{ Hz, 2H}), 2.25 \ (m, 1H), 1.96 \ (m, 1H), 1.72 \ (m, 2H), 1.60-0.95 \ (br, 45H), 1.08 \ (s, 9H), 0.91 \ (m, 9H), 0.86 \ (d, \ J = 6.5 \text{ Hz, 3H}), 0.83 \ (d, \ J = 6.5 \text{ Hz, 3H}), 0.76 \ (d, \ J = 6.5 \text{ Hz, 3H}), 0.69 \ (d, \ J = 6.4 \text{ Hz, 3H}); \(^{13}\text{C}-\text{NMR} (\text{CDCl}_3, 100.6 \text{ MHz})\) \(\delta 190.13 \ (s), 144.34 \ (d), (136.31, 136.27) \ (d, 4 \times C), (135.16, 134.82) \ (s, 2 \times C), 130.12 \ (d), (129.60, 129.50) \ (d, 2 \times C), (127.57, 127.49) \ (d, 4 \times C), 76.95 \ (d), 45.27 \ (t), 45.15 \ (t), 45.12 \ (t), 44.40 \ (t), 40.59 \ (t), 38.99 \ (t), 35.69 \ (d), 31.93 \ (t), 31.70 \ (t), 29.96 \ (d), 29.71 \ (t, 6 \times C), 29.67 \ (t), 29.56 \ (t), 29.54 \ (t), 29.37 \ (t), 27.67 \ (d), 27.50 \ (d), 27.48 \ (d), 27.41 \ (d),
\end{align*}\)\]

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The title compound was prepared from 33b following procedure A. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 34 as a colorless oil (495 mg, 94%). \([\alpha]_D = +6.8^\circ (c = 1.46, \text{ CHCl}_3)\). 1H-NMR (400 MHz, CDCl₃): \(\delta\) 7.69 (m, 4H), 7.38 (m, 6), 3.59 (m, 1H), 2.88 (q, \(J = 7.4\) Hz, 2H), 2.57 (dd, \(J = 5.0, 14.3\) Hz, 1H), 2.27 (dd, \(J = 8.7, 14.2\) Hz, 1H), 2.13 (m, 1H), 1.69 (m, 1H), 1.60-0.95 (br, 48H), 1.07 (s, 9H), 0.95 (d, \(J = 6.6\) Hz, 3H), 0.89 (m, 9H), 0.84 (d, \(J = 5.2\) Hz, 3H), 0.83 (d, \(J = 5.1\) Hz, 3H), 0.76 (d, \(J = 6.5\) Hz, 3H), 0.69 (d, \(J = 6.4\) Hz, 3H); \(^{13}\)C-NMR (CDCl₃, 100.6 MHz) \(\delta\) 199.22 (s), (136.06, 136.02) (d, 4 x C), (134.92, 134.57) (s, 2 x C), (129.35, 129.25) (d, 2 x C), (127.32, 127.24) (d, 4 x C), 76.70 (d), 50.95 (t), 45.26 (t), 45.21 (t), 45.15 (t), 45.11 (t), 44.45 (t), 40.58 (t), 35.70 (d), 31.93 (t), 31.70 (t), 29.71 (t, 6 x C), 29.67 (t), 29.56 (t), 29.54 (t), 29.37 (t), 28.68 (d), 27.69 (d), 27.53 (d, 3 x C), 27.44 (d), 27.17 (q, 3 x C), 26.37 (t), 23.25 (t), 22.69 (t), 21.39 (q, 2 x C), 21.33 (q), 21.24 (q), 20.82 (q), 20.57 (q), 19.54 (s), 15.31 (q), 14.81 (q), 14.12 (q). HRMS(ESI+) calculated for C₃₂H₉₈O₅Si (M + Na⁺) 885.6954, found 885.6946.


The title compound was prepared from 34 following procedure B and C. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 34b as a colorless oil (380 mg, 75%). \([\alpha]_D = +9.3^\circ (c = 1.08,\)
CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 7.68 (m, 4H), 7.38 (m, 6H), 6.88 (m, 1H), 6.11 (dt, J = 1.0, 15.4 Hz, 1H), 3.58 (m, 1H), 2.95 (q, J = 7.4 Hz, 2H), 2.24 (m, 1H), 1.95 (m, 1H), 1.71 (m, 2H), 1.60-0.95 (br, 48H), 1.07 (s, 9H), 0.80-0.92 (m, 18H) 0.75 (d, J = 6.5 Hz, 3H), 0.68 (d, J = 6.3 Hz, 3H); ¹³C-NMR (CDCl₃, 100.6 MHz) δ 189.93 (s), 144.14 (d), 136.06, 136.02 (d, 4 x C), 134.91, 134.56 (s, 2 x C), 129.86 (d), 129.36, 129.25 (d, 2 x C), 127.32, 127.25 (d, 4 x C). 76.68 (d), 45.26 (t), 45.24 (t), 45.14 (t), 45.09 (t), 44.39 (t), 40.57 (t), 38.99 (t), 35.68 (d), 31.93 (t), 31.69 (t), 29.95 (d), 29.72 (t, 5 x C), 29.67 (t), 29.57 (t), 29.55 (t), 29.37 (t), 27.65 (d), 27.50 (d, 4 x C), 27.45 (d), 27.17 (q, 3 x C), 26.37 (t), 23.01 (t), 22.70 (t), 21.39 (q), 21.36 (q), 21.32 (q), 21.28 (q), 20.89 (q), 20.56 (q), 19.54 (s), 15.30 (q), 14.83 (q), 14.13 (q). HRMS(ESI+) calculated for C₅₈H₁₀₀O₂Si (M + Na⁺) 911.7111, found 911.7105.


The title compound was prepared from 34b following procedure A. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 35 as a colorless oil (336 mg, 90%). [α]D = +7.6° (c = 1.34, CHCl₃). ¹H-NMR (400 MHz, CDCl₃): δ 7.69 (m, 4H), 7.38 (m, 6H), 3.59 (m, 1H), 2.89 (q, J = 7.2 Hz, 2H), 2.57 (dd, J = 5.0, 14.3 Hz, 1H), 2.27 (dd, J = 8.7, 14.2 Hz, 1H), 2.14 (m, 1H), 1.70-0.95 (br, 52H), 1.07 (s, 9H), 0.95 (m, 1H), 1.70-0.95 (br, 52H), 1.07 (s, 9H), 0.95 (m, 1H), 1.70-0.95 (br, 52H), 1.07 (s, 9H), 0.95 (m, 1H), 1.70-0.95 (br, 52H), 1.07 (s, 9H), 0.95 (m, 1H), 1.70-0.95 (br, 52H), 1.07 (s, 9H), 0.95 (m, 1H). HRMS(ESI+) calculated for C₅₈H₁₀₀O₂Si (M + Na⁺) 927.7424, found 927.7420.
mmol, solution in ether) was carefully added to a stirred solution of Cul (1.180 mmol) in diethyl ether (8 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred for 10 min and was then cooled down to −70 °C. Substrate 35 (0.236 mmol) in 2 mL diethyl ether was added in a dropwise fashion. The reaction mixture was stirred for 16 h and was quenched with a saturated aq. solution of NH₄Cl. The organic layer was separated and the aqueous layer was extracted with three portions of 15 ml diethyl ether. The combined organic layers were dried on MgSO₄ and the solvents evaporated under reduced pressure. The crude material was purified by flash chromatography (eluent pentane/ether 40:1) to afford 38 as a colorless oil (170 mg, 84%). [α]D = +6.0° (c = 1.60, CHCl₃). 1H-NMR (400 MHz, CDCl₃): δ 7.69 (dd J = 1.3, 7.8 Hz, 4H), 7.37 (m, 6H), 3.58 (m, 1H), 2.44 (dd, J = 3.4, 14.5 Hz, 1H), 2.11 (m, 4H), 1.68 (m, 1H), 1.65-0.95 (br, 52H), 1.07 (s, 9H), 0.91-0.83 (m, 18H), 0.76 (d, J = 6.5 Hz, 3H), 0.69 (d, J = 6.4 Hz, 3H). 13C-NMR (CDCl₃, 100.6 MHz) δ 209.08 (s), (136.05, 136.02) (d, 4 x C), (134.90, 134.55) (s, 2 x C), (129.35, 129.25) (d, 2 x C), (127.24) (d, 4 x C), 76.67 (d), 50.81 (t), 45.23 (t), 45.14 (t), 45.13 (t), 45.09 (t), 44.67 (t), 40.57 (t), 35.67 (d), 31.92 (t), 31.67 (t), 30.43 (d), 29.70 (t, 7 x C), 29.67 (t), 29.56 (t), 29.54 (t), 29.36 (t), 27.65 (d), 27.58 (d, 2 x C), 27.51 (d, 2 x C), 27.45 (d), 27.41 (q, 3 x C), 26.83 (q), 26.36 (t), 22.69 (t), 21.44 (q), 21.42 (q), 21.38 (q), 21.32 (q), 21.26 (q), 20.87 (q), 20.80 (q), 19.54 (s), 15.30 (q), 14.12 (q). HRMS(ESI+) calculated for C₈₉H₁₆₂O₂Si (M + Na⁺) 881.7547, found 881.7542.

(+)-(2S,4S,6S,8S,10S,12R,14R,16R,17S)-17-(t-Butyldiphenylsilyloxy)-2,4,6,8,10,12,14,16-octamethyldotriacontyl acetate (39)

ketone 38 (0.076 mmol) was dissolved in 2 mL CH₂Cl₂, mCPBA (0.152
mmol) was added and the reaction mixture was stirred for 3 d at rt. An additional 2 equiv. of mCPBA (0.152 mmol) were added after 3 d and the mixture was stirred for 2 additional days. The product partially hydrolysed under the reaction conditions. The solvent was evaporated and the crude reaction mixture was used in the next step (hydrolysis) directly. The crude material can be purified by flash chromatography (eluent pentane/ether 40:1) to afford 39 as a colorless oil \([\alpha]_D = +8.3^\circ \) (c = 0.99, CHCl\(_3\)). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 7.68 \) (dd, \(J = 1.5, 7.9 \) Hz, 4H), 7.37 (m, 6H), 3.98 (dd, \(J = 5.0, 10.7 \) Hz, 1H), 3.83 (dd, \(J = 7.0, 10.7 \) Hz, 1H), 3.58 (m, 1H), 2.05 (s, 3H), 1.90 (m, 1H), 1.65-0.90 (br, 52H), 1.07 (s, 9H), 0.94 (d, \(J = 6.7 \) Hz, 3H), 0.90-0.92 (m, 15H), 0.75 (d, \(J = 6.5 \) Hz, 3H), 0.68 (d, \(J = 6.5 \) Hz, 3H); \(^1^3\)C-NMR (CDCl\(_3\), 100.6 MHz) \(\delta 171.23 \) (s), (136.06, 136.03) (d, 4 x C), (134.93, 134.58) (s, 2 x C), (129.35, 129.25) (d, 2 x C), (127.32, 127.24) (d, 4 x C), 76.67 (d), 69.17 (t), 45.28 (t), 45.26 (t), 45.16 (t), 45.11 (t), 41.00 (t), 40.58 (t), 35.69 (t), 31.92 (t), 31.71 (t), 29.94 (d), 29.71 (t, 7 x C), 29.67 (t), 29.56 (t), 29.54 (t), 29.36 (t), 27.68 (d), 27.57 (d, 2 x C), 27.54 (d, 2 x C), 27.48 (d), 27.17 (q, 3 x C), 26.37 (t), 22.69 (t), 21.43 (q), 21.38 (q, 2 x C), 21.32 (q), 21.16 (q), 21.00 (q), 20.93 (q), 19.54 (q), 18.17 (q), 15.31 (q), 14.11 (q); HRMS(ESI\textsuperscript{+}) calculated for C\(_{58}\)H\(_{102}\)O\(_3\)Si (M + Na\(^+\)) 897.7496, found 897.7491.

\((+)-(2S,4S,6S,8S,10R,12R,14R,16R,17S)-17-(t-Butyldiphenylsilyloxy)-2,4,6,8,10,12,14,16-octamethyldotriacontan-1-ol (40)\)

![Diagram of the compound](image)

Crude 39 was dissolved in a mixture of THF/MeOH/H\(_2\)O (60/30/10, 4 mL total volume), 10 equiv. of KOH (43 mg, 0.760 mmol) were added and the mixture was stirred for 16 h at rt. Diethyl ether (10 mL) and H\(_2\)O (4 mL) were added. The organic layer was separated and the water layer was extracted with three portions of 15 ml diethyl ether. The combined organic layers were dried on MgSO\(_4\) and the solvent evaporated under reduced pressure. The crude material was purified by flash chromatography (eluent pentane/ether 9:1) to afford 40 as a waxy oil (40 mg, 63% over 2 steps). \([\alpha]_D = +4.1^\circ \) (c = 1.13, CHCl\(_3\)). \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta 7.69 \) (dd, \(J = 1.2, 6.7 \) Hz, 4H), 7.37 (m, 6H), 3.54 (m, 1H), 3.56 (dd, \(J = 4.9, 10.4 \) Hz, 1H), 3.38 (dd, \(J = 6.9, 10.4 \) Hz, 1H), 1.80-0.90 (br, 54H), 1.07 (s, 9H), 0.95 (d, \(J = 6.7 \) Hz, 3H),
0.91-0.83 (m, 15H), 0.76 (d, J = 6.5 Hz, 3H), 0.69 (d, J = 6.4 Hz, 3H); $^{13}$C-NMR (CDCl₃, 100.6 MHz) δ (136.07, 136.03) (d, 4 x C), (134.93, 134.58) (s, 2 x C), (129.35, 129.25) (d, 2 x C), (127.32, 127.24) (d, 4 x C), 76.67 (d), 68.12 (t), 45.28 (t, 2 x C), 45.16 (t), 45.12 (t), 40.92 (t), 40.59 (t), 35.70 (d), 33.10 (d), 31.93 (t), 31.70 (t), 29.71 (t, 7 x C), 29.67 (t), 29.57 (t), 29.55 (t), 29.37 (t), 27.70 (d), 27.65 (d, 4 x C), 27.58 (d), 27.17 (q, 3 x C), 26.37 (t), 22.69 (t), 21.46 (q, 2 x C), 21.39 (q), 21.33 (q, 2 x C), 21.18 (q), 19.55 (s), 17.73 (q), 15.31 (q), 14.12 (q). HRMS (ESI⁺) calculated for C₅₉H₁₀₀O₂Si (M + Na⁺) 855.7390, found 855.7382.

(+)-(2S,4S,6S,8S,10R,12R,14R,16R,17S)-Methyl 17-(t-butyldiphenylsilyloxy)-2,4,6,8,10,12,14,16-octamethylidotriacontanoate (41)

To a stirred mixture of 40 (70 mg, 0.084 mmol) in 1.2 mL CCl₄, 1.2 mL CH₃CN and 2.4 mL H₂O was added RuCl₃·(H₂O)₃ (1.0 mg, 0.005 mmol) and NaIO₄ (51.4 mg, 0.218 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 the crude acid, which was directly converted into methyl ester 41. The acid was dissolved in methanol (3 mL) and trimethylsilyldiazomethane (0.252 mmol, solution in diethyl ether) was added and the reaction mixture was stirred for 30 min at rt. The solvents were evaporated and the crude material was purified by flash chromatography (eluent pentane/ether 9:1) to afford 41 as a colorless oil (54.3 mg, 75%). [α]D = +14.9° (c = 1.33, CHCl₃). $^{1}$H-NMR (400 MHz, CDCl₃): δ 7.68 (m, 4H), 7.37 (m, 6H), 3.67 (s, 3H), 3.58 (m, 1H), 2.58 (m, 1H), 1.75-0.90 (br, 56H), 1.16 (d, J = 6.9 Hz, 3H), 1.06 (s, 9H), 0.90-0.82 (m, 15H), 0.75 (d, J = 6.6 Hz, 3H), 0.68 (d, J = 6.6 Hz, 3H); $^{13}$C-NMR (CDCl₃, 100.6 MHz) δ 177.40 (s), (136.06, 136.02) (d, 4 x C), (134.91, 134.56) (s, 2 x C), (129.35, 129.25) (d, 2 x C), (127.32, 127.24) (d, 2 x C), 76.68 (d), 51.36 (q), 45.35 (t), 45.32 (t), 45.14 (t), 45.09 (t), 45.03 (t), 40.95 (t), 40.57 (t), 37.38 (d), 35.66 (d), 31.93 (t), 31.68 (t), 29.71 (t, 8 x C), 29.67 (t), 29.56 (t), 29.54 (t), 29.37 (t), 28.22 (d), 27.64 (d), 27.49 (d, 2 x C), 27.42 (d), 27.22 (d), 27.16 (q, 3 x C), 26.36 (t), 22.69 (t), 21.36 (q, 2 x C), 21.31
(q), 21.23 (q), 20.83 (q), 20.58 (q), 19.54 (s), 18.31 (q), 15.29 (q), 14.12 (q). HRMS(ESI+) calculated for $\text{C}_{25}\text{H}_{100}\text{O}_3\text{Si} (M + Na^+)$ 883.7333, found 883.7333.

(+)-(2S,4S,6S,8S,10R,12R,14R,16R,17S)-Methyl 17-hydroxy-2,4,6,8,10,12,14,16-octamethyltriocatantoate (anti-9)

To a stirred mixture of 41 (22 mg, 0.025 mmol) in THF (2 mL) at rt under nitrogen was added TBAF (0.075 mL, 0.075 mmol, 1.0 M solution in THF), and the mixture was stirred for 2 d. The reaction mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography (eluent pentane/ether 9:1) to afford anti-9 as a colorless oil (11.2 mg, 72%). $[\alpha]_D = +17^\circ$ (c = 0.99, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.66 (s, 3H), 3.47 (m, 1H), 2.57 (m, 1H), 1.75-0.90 (br, 53H), 1.15 (d, $J = 6.9$ Hz, 3H), 0.86 (m, 21H). $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) $\delta$ 177.43 (s), 75.73 (d), 51.39 (q), 45.36 (t), 45.32 (t), 45.18 (t), 45.08 (t), 40.95 (t), 40.10 (t), 37.38 (d), 36.26 (d), 32.72 (t), 31.92 (t), 29.76 (t), 29.69 (t, 9 x C), 29.36 (t), 28.23 (d), 27.95 (d), 27.72 (d), 27.64 (d), 27.49 (d), 27.25 (d), 26.29 (t), 22.69 (t), 21.55 (q), 21.52 (q), 21.47 (q), 21.27 (q), 20.84 (q), 20.58 (q), 18.31 (q), 15.84 (q), 14.12 (q). HRMS(ESI+) calculated for $\text{C}_{41}\text{H}_{80}\text{O}_2 (M - H_2\text{O})$ 605.6231, found 605.6260.

(+)-(2S,4S,6S,8S,10R,12R,14R,16R,17R)-Methyl 17-hydroxy-2,4,6,8,10,12,14,16-octamethyltriocatantoate (syn-9)

To a solution of anti-9 (6 mg, 0.010 mmol), DEAD (diethylazadicarboxylate, 0.044 mmol) and triphenylphosphine (0.038 mmol) in 0.5 mL toluene, p-nitrobenzoic acid (0.039 mmol) was added and the mixture was stirred for 48 h at rt under nitrogen atmosphere. The solvent was evaporated and the crude product was dissolved in 2 mL MeOH. A catalytic amount of NaCN (0.005 mmol) was added and the mixture was stirred for 16 h at rt. The solvent was evaporated and the crude material was purified by flash chromatography (eluent pentane/ether 9:1) to afford syn-9 as a colorless oil (5.1 mg, 85%). $[\alpha]_D = +16^\circ$ (c = 0.30, CHCl$_3$). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 3.66 (s, 3H), 3.51 (m, 1H), 2.57 (m, 1H), 1.75-0.90 (br, 53H), 1.15 (d, $J =$
6.9 Hz, 3H), 0.86 (m, 21H). $^1$H-NMR (CDCl$_3$, 100.6 MHz) $\delta$ 177.43 (s), 74.37 (s), 45.36 (t), 45.30 (t), 45.08 (t), 41.15 (t), 40.99 (t), 37.39 (d), 35.08 (d), 34.89 (t), 31.92 (t), 29.76 (t), 29.68 (t), 29.35 (t), 28.26 (d), 27.62 (d), 27.50 (d), 27.29 (d), 26.36 (t), 22.68 (t), 21.41 (q), 21.27 (q), 21.23 (q), 20.85 (q), 20.57 (q), 18.29 (q), 14.11 (q), 14.00 (q). HRMS(ESI+) calculated for C$_{41}$H$_{80}$O$_2$ (M – H$_2$O) 605.6231, found 605.6255.
6.7 References


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