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Tetrahedron
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Tetrahedron 62 (2006) 3221–3227

An improved procedure for the preparation of the β-hydroxy-α-alkyl fatty acid fragment of mycolic acids

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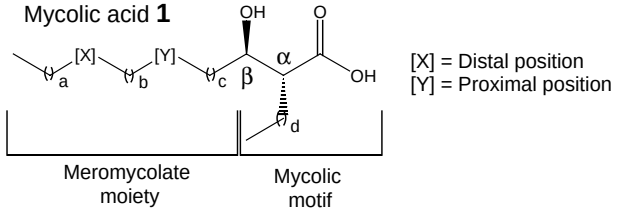
Received 25 November 2005; revised 29 December 2005; accepted 19 January 2006

Abstract—An approach to a β-hydroxy-α-alkyl fatty acid intermediate that can be applied in the synthesis of a range of mycolic acids is described.

1. Introduction

Mycolic acids (**1**) (Scheme 1), are major constituents of the cell envelope of *Mycobacterium tuberculosis* and other mycobacteria, some of which are pathogenic to animals and humans.[1,2] Their presence is thought to be linked to the characteristic resistance of these organisms to most current antibiotics and other chemotherapeutic agents.[3] In every mycolic acid two moieties can be distinguished: the meromycolate and the mycolic motif. The structure of the mycolic motif is common to each mycobacterial mycolic acid, except for minor variations in the length of the chain in the α-position (d). The meromycolate moiety, however, is much more variable.[4,5]



Scheme 1.

The two stereocentres in the α and β-positions relative to the carboxylic group have both been found to be in the *R*-configuration for all the mycolic acids examined, irrespective of the other functional groups contained in the meromycolate moiety.[6–10]

The presence of the hydroxyl group and the relative configuration between it and the alkyl chain has been demonstrated to be capable of altering the film molecular packing. The formation of a hydrogen bond between the hydroxyl group and the carboxylic group has a stabilising effect for the aligned conformation between the two long chains.[11,12] Minnikin first proposed that, for the same reasons, the mycolic motif allows the formation of a closely packed structure among the mycolic acids in the cell wall of mycobacteria.[1,2] Moreover, the absolute configuration of these two chiral centres is necessary for efficient recognition by T cells and the generation of an immune response by the host organism against pathogenic mycobacteria;[13] the same is also true for the antitumour properties of mycolic acid derivatives.[14] This motif is therefore critical in defining some physical and biological properties of these particular fatty acids.

While different methods for the synthesis of single enantiomers of corynomycolic acids (**2**) have been proposed,[15–20] the preparation of the functionalised analogue (**3**) has only recently been reported (Scheme 2).[21] The potential of this compound in the preparation of enantiomerically pure mycolic acids (**1**) has also been illustrated. [21] However, the C-24 chain of (**3**) is not readily available in large quantities and had first to be prepared by coupling two smaller units.

2. Results and discussion

This paper proposes a new method for the synthesis of an alternative intermediate (**11**) for the preparation of any mycolic acid (Scheme 4) which allows any alkyl chain or labelled alkyl chain to be introduces at the β-position.

The β-hydroxy ester (**10**) was prepared following a similar method to that described for the preparation of *R*-α-lipoic acid (Scheme 3).[22] The *E*-α,β-unsaturated ester (**7**),

Keywords: Mycolic acid synthesis.
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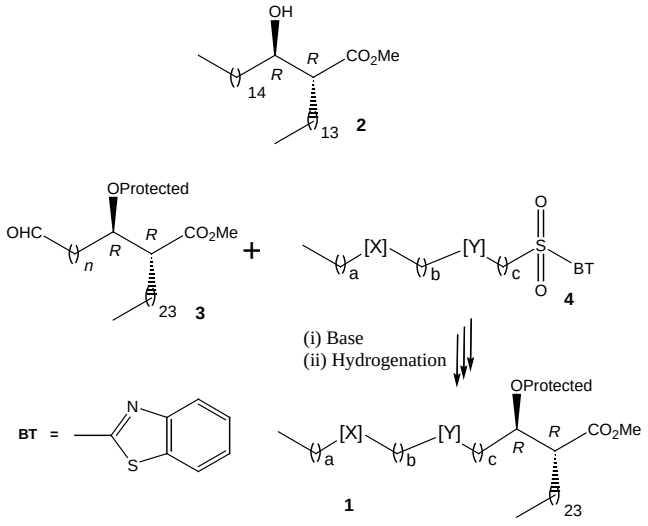
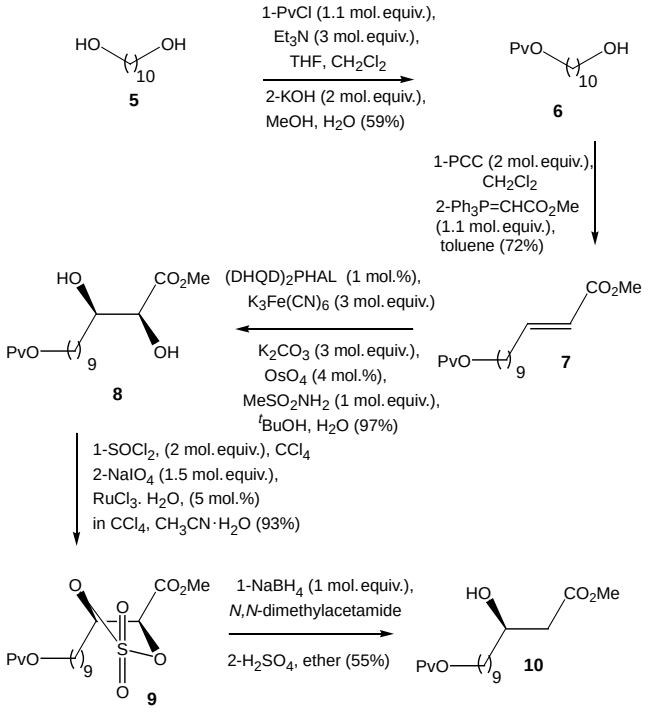
doi:10.1016/j.tet.2006.01.070



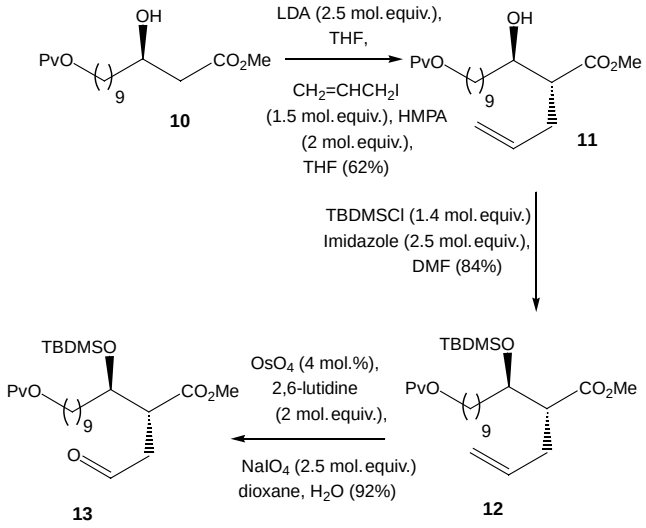
Scheme 2.



Scheme 3.

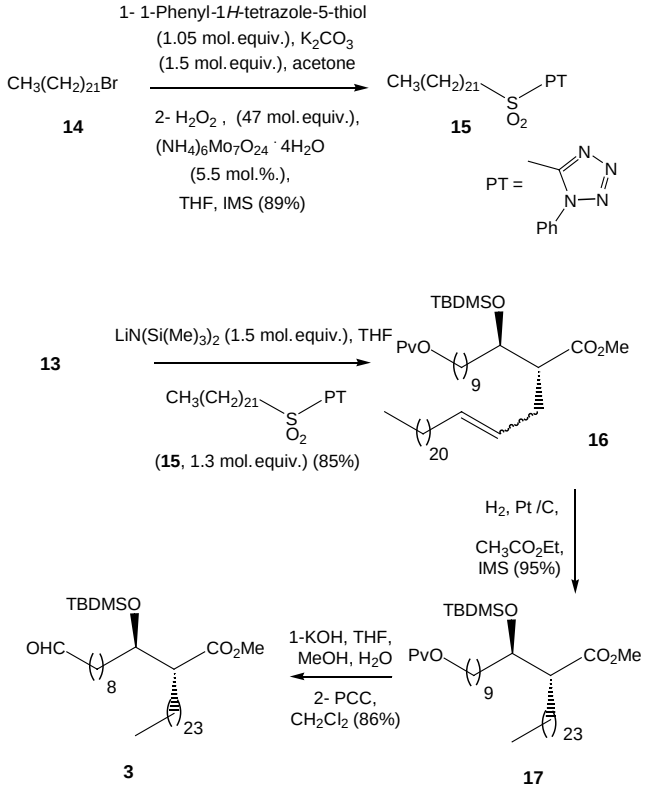
prepared from the diol (**5**), was transformed into the diol (**8**) using a Sharpless dihydroxylation.[23] The diol was then converted into the cyclic sulfate (**9**) via cyclic sulfite.[24] The sulfate (**9**) was regioselectively reduced and hydrolysed to give the (3*R*)-3-hydroxy ester (**10**).

Subsequently, a Fräter alkylation with allyl iodide introduced an allyl chain at the α-position to give (2*R*,3*R*)-2-allyl-3-hydroxy ester (**11**) (Scheme 4).[25,26] The use of such a reactive electrophile resulted in a much more reliable reaction than that previously described,[21] which used a very long chain alkyl iodide. It also gave twice the best yield achieved with a long chain.[21] Nonetheless, it was still very sensitive to the precise conditions and sometimes produced a minor isomer apparently derived by allylation on oxygen.[27]



Scheme 4.

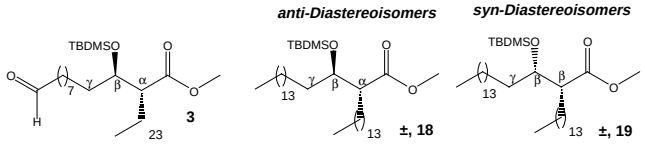
After having protected the secondary alcohol (**11**), an OsO_4–$NaIO_4$ oxidation transformed the alkene (**12**) into the corresponding aldehyde (**13**). The reaction was carried out in the presence of 2,6-lutidine, since it has been reported that this base suppresses side reactions, improving the cleavage of the olefin.[28] A Julia reaction with the 1*H*-tetrazole (**15**) (Scheme 5), followed by reduction of the unsaturated intermediate (**16**), allowed the formation of the desired long chain at the β-position.[29] Finally, deprotection of the terminal alcohol in the diol (**17**) and its oxidation gave the required compound (**3**).



Scheme 5.

Through NMR comparison of compound (**3**) with the *anti*- and *syn*-corynomycolate derivatives (**18** and **19**), prepared as described by Datta et al.,[30] it was possible to show that the α-alkyl-β-hydroxy groups were still in *anti*-configuration to each other (Table 1). Thus, the use of different bases in the process for the elongation of the α-branch did not produce epimerisation at the α-position via enol-formation, as has been described when other basic conditions were employed.[12,31]

Table 1.



Atom	β-Hydroxy-α-alkyl acid (**3**) (ppm)	*anti*-Diastereoisomer (**18**) (ppm)	*syn*-Diastereoisomer (**19**) (ppm)
C=O	175.0	175.1	175.2
Cα	51.6	51.6	51.5
Cβ	73.2	73.2	73.4
Cγ	33.7	33.7	34.8
Hα	2.53 (ddd, J=10.9, 7.0, 3.8 Hz)	2.53 (ddd, J=10.7, 7.0, 3.8 Hz)	2.48 (dt, J=9.8, 5.7 Hz)

This method was based on the formation of alkene (**12**), which was obtained with a good yield and could be readily transformed into any desired α-alkyl-β-hydroxy ester. Through formation of aldehydes (**13**) and (**3**) and their subsequent coupling with heterocyclic sulfones, every α-branch or meromycolate chain, including labelled compounds, can easily be introduced at different points of the synthesis. Therefore, this method could be used for the production not only of any natural mycolic acid as a single enantiomer, but also of intermediates useful for studies of the biosynthesis of these fatty acids.

3. Experimental

3.1. General

All chemicals were purchased from Aldrich Chemical Co. Ltd, Lancaster Synthesis Ltd, or Avocado Chemical Co. Ltd. THF was distilled over sodium and benzophenone under nitrogen, while dichloromethane was distilled over calcium hydride. Petrol refers to the fraction bp 40–60 °C. Organic solutions were dried over anhydrous magnesium sulfate and solvents were removed at 14 mmHg; residual traces of solvent were finally removed at 0.1 mmHg. All glassware used in anhydrous reactions was dried for not less than 5 h in a 250 °C oven.

Column chromatography was conducted under medium pressure using silica gel (BDH, particle size 33–70 μm); TLC was carried out on pre-coated Kieselgel 60 F254 (Art. 5554; Merck) plates. Optical rotations were measured as solutions in chloroform of known concentration using a Polar 2001 automatic polarimeter. Infra-red spectra were recorded as KBr discs (solids) or thin films on NaCl windows or using a Perkin Elmer 1600 series FT-IR spectrometer. NMR spectra were recorded on a Bruker Advance 500 spectrometer as solutions in deuterated chloroform ($CDCl_3$) if not differently indicated. Chemical shifts are quoted in δ relative to chloroform (δ 7.27 ppm), and $CDCl_3$ (δ 77.0 ppm). Mass spectra were obtained using a Bruker MicroTOF time of flight mass spectrometer with ESI source. The accurate mass of compound (**3**) was obtained using a Bruker APEX IV FT ICR mass spectrometer with a 4.7 T magnet with ESI source.

3.1.1. 2,2-Dimethylpropionic acid 10-hydroxydecyl ester. Trimethylacetyl chloride (13.2 g, 110 mmol) was added to a solution of 1,10-decanediol (**5**, 17.4 g, 100 mmol) and triethylamine (30 g, 300 mmol) in dry THF (300 ml) and CH_2Cl_2 (400 ml) at 5 °C. The mixture was monitored by TLC and quenched with dil HCl (2 N, 200 ml) after 3 h. The product was extracted with dichloromethane (3×500 ml) and the combined organic layers were washed with water (100 ml), dried and the solvent evaporated. The product was then purified by chromatography eluting with petrol–ether (1/1) to give 2,2-dimethylpropionic acid 10-hydroxydecyl ester (**6**, 12.6 g, 49%), which has been partly described,[32] which showed δ_H: 4.01 (2H, t, J=6.6 Hz, CH_2OCO), 3.60 (2H, br t, J=6.6 Hz, CH_2OH), 2.2–2.0 (1H, m, OH), 1.7–1.6 (2H, m), 1.6–1.5 (2H, m), 1.4–1.2 (13H, m), 1.16 (9H, s (CH_3)$_3$); δ_C: 178.63 (C=O), 64.39 (CH$_2$OC=O), 62.80 (CH$_2$OH), 38.65 (C(CH$_3$)$_3$), 29.19 (CH$_2$), 28.96 (CH$_2$), 28.52 (CH$_2$), 27.24 (CH$_2$), 27.12 (C(CH$_3$)$_3$), 26.97 (CH$_2$); ν_{max}/cm^{-1}: 3393, 2929, 1732, 1458, 1285, 1158, 1056 (Found (M+H)$^+$: 259.2258; $C_{15}H_{31}O_3$ requires: 259.2268). The diprotected compound, 2,2-dimethylpropionic acid 10-(2,2-dimethylpropionyloxy)decyl ester (**20**, 6 g, 18%) was also obtained as an oil, which showed δ_H: 4.00 (4H, t, J=6.7 Hz, CH$_2$OCO), 1.7–1.5 (4H, m), 1.4–1.2 (12H, m), 1.14 (18H, s (CH_3)$_3$); δ_C: 178.50 (C=O), 64.33 (CH$_2$OC=O), 38.65 (C(CH$_3$)$_3$), 29.19 (CH$_2$), 28.96 (CH$_2$), 28.52 (CH$_2$), 27.24 (CH$_2$), 27.12 (C(CH$_3$)$_3$), 26.97 (CH$_2$); ν_{max}/cm^{-1}: 2930, 1730, 1480, 1284, 1155 (Found (M+H)$^+$: 343.2844; $C_{20}H_{39}O_4$ requires: 343.2843). This was added to a solution of KOH (1.9 g, 34 mmol) in methanol (100 ml) and water (5 ml). The mixture was refluxed for 1.5 h, monitoring by TLC, then evaporated. The residue was dissolved in water (50 ml) and extracted with dichloromethane (3×75 ml). The combined organic layers were dried and evaporated to give the crude product; chromatography eluting with 1:1 petrol and ether gave 2,2-dimethylpropionic acid 10-hydroxydecyl ester (**6**, 2.5 g, 57%) which showed the same NMR spectra as those above. Combining the two reactions, gave (**6**) (59%).

3.1.2. (*E*)-12-(2,2-Dimethylpropionyloxy)dodec-2-enoic acid methyl ester (7). The alcohol (**6**, 15 g, 58 mmol) in dichloromethane (40 ml) was added to PCC (25 g, 116 mmol) in dichloromethane (800 ml) and vigorously stirred for 2 h when TLC showed no starting material, then quenched by diluting with ether (500 ml) and filtered on a pad of Celite and silica. Evaporation and chromatography using petrol and ether (10:1) to give 2,2-dimethylpropionic acid 10-oxodecyl ester (**21**, 12.4 g, 84%) as an oil, δ_H: 9.73 (1H, br t, J=1.6 Hz, CHO), 4.04 (2H, t, J=6.4 Hz, CH_2OCO), 2.39 (2H, br td, J_1=1.6 Hz, J_2=ca. 7.3 Hz, CH_2CHO), 1.59 (2H, m), 1.4–1.2 (12H, m), 1.16 (9H, s (CH_3)$_3$); δ_C: 202.67 (CH=O), 178.52 (C=O), 64.31

(CH_2OCO), 43.80 ($CH_2CH{=}O$), 38.65 ($C(CH_3)_3$), 29.19 (CH_2), 29.17 (CH_2), 29.03 (CH_2), 28.52 (CH_2), 27.24 (CH_2), 27.12 ($C(CH_3)_3$), 25.78 (CH_2), 21.97 (CH_2); ν_{max}/cm^{-1}: 2928, 1728, 1458, 1285, 1155.

The aldehyde (**21**, 12.2 g, 48 mmol) was dissolved in toluene (20 ml) and then added to a suspension of (methoxycarbonylmethylene)triphenylphosphorane (18 g, 54 mmol) in toluene (100 ml). The mixture was stirred overnight, then the solvent was evaporated to give a white solid. This was refluxed for 1 h with petrol and ether (1:1, 300 ml) then filtered and the precipitate washed with the same solution (150 ml). The combined organic layers were dried and evaporated. Chromatography eluting with petrol and ether (10:1) gave (*E*)-12-(2,2-dimethylpropionyloxy)-dodec-2-enoic acid methyl ester (**7**, 12.8 g, 86%) as a pale yellow oil, which showed δ_H: 6.97 (1H, dt, $J_1=15.5$ Hz, $J_2=6.9$ Hz, C*H*=$CHCO_2Me$), 5.81 (1H, d, $J=15.5$ Hz, CH=C*H*CO_2Me), 4.04 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.72 (3H, s, OCH_3), 2.25–2.15 (2H, m), 1.7–1.6 (2H, m), 1.5–1.4 (2H, m), 1.4–1.2 (10H, m), 1.19 (9H, s $(CH_3)_3$); δ_C: 178.61 (*C*=O), 167.16 (*C*=O), 149.71 (*C*H=$CHCO_2Me$), 120.83 (CH=*C*HCO_2Me), 64.39 (CH_2OCO), 51.33 (OCH3), 38.70 ($C(CH_3)_3$), 32.16 (CH_2), 29.34 (CH_2), 29.25 (CH_2), 29.14 (CH_2), 29.05 (CH_2), 28.58 (CH_2), 27.97 (CH_2), 27.18 ($C(CH_3)_3$), 25.86 (CH_2); ν_{max}/cm^{-1}: 2928, 2856, 1728, 1658, 1284, 1157 (Found $(M+H)^+$: 313.2369; $C_{18}H_{33}O_4$ requires: 313.2373).

3.1.3. (2*S*,3*R*)-12-(2,2-Dimethylpropionyloxy)-2,3-dihydroxydodecanoic acid methyl ester (8). The $(DHQD)_2PHAL$ ligand (313 mg, 0.4 mmol), $K_3Fe(CN)_6$ (39.6 g, 120 mmol), K_2CO_3 (16.8 g, 120 mmol) and a solution 2.5% of OsO_4 in *tert*-butanol (2.0 ml, 1.6 mmol) were dissolved in 1:1 water and *tert*-butanol (380 ml) at room temperature. $MeSO_2NH_2$ (3.8 g, 40 mmol) was added and the mixture, vigorously stirred, was cooled to 2.5 °C when the alkene (**7**, 12.5 g, 40 mmol) was added. The reaction was maintained at this temperature and monitored by TLC. After 8 h, it was worked up by addition of sodium sulfite (60 g, 48 mmol), then warmed to room temperature for 45 min and extracted with dichloromethane (3×500 ml); the organic layers were washed with 2 N KOH (100 ml), dried and concentrated to give an oil. Chromatography using 7:3 petrol and ether gave (2*S*,3*R*)-12-(2,2-dimethylpropionyloxy)-2,3-dihydroxydodecanoic acid methyl ester (**8**, 13.4 g, 97%) as an oil; δ_H: 4.10 (1H, dd, $J_1=5.3$ Hz, $J_2=1.9$ Hz, C*H*OH), 4.04 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.95–3.85 (1H, m, C*H*OH), 3.83 (3H, s, OCH_3), 3.3–3.2 (1H, br s, O*H*), 2.1–2.0 (1H, br s, O*H*), 1.6–1.5 (4H, m), 1.5–1.2 (12H, m), 1.12 (9H, s $(CH_3)_3$); δ_C: 178.67 (*C*=O), 174.07 (*C*=O), 73.07 (*C*HOH), 72.45 (*C*HOH), 64.42 (CH_2OCO), 52.78 (OCH_3), 38.71 ($C(CH_3)_3$), 33.71 (CH_2), 29.38 (CH_2), 29.14 (CH_2), 28.57 (CH_2), 27.18 ($C(CH_3)_3$), 25.85 (CH_2), 25.65 (CH_2); ν_{max}/cm^{-1}: 3493, 2932, 2858, 1728, 1285, 1157; $[\alpha]_D^{19}$ +11.5 (*c* 1.0, $CHCl_3$), (lit. $[\alpha]_D^{24}$ +11.4 (*c* 0.57, $CHCl_3$) for (2*S*,3*R*)-2,3-dihydroxydecanoic acid ethyl ester)[33] (Found $(M+H)^+$: 347.2425; $C_{18}H_{35}O_6$ requires: 347.2428).

3.1.4. (4*S*,5*R*)-5-[9-(2,2-Dimethylpropionyloxy)nonyl]-2,2-dioxo-2λ^6-[1,3,2]dioxathiolane-4-carboxylic acid methyl ester (9). The dihydroxy ester (**8**, 5 g, 14.4 mmol) was dissolved in CCl_4 (20 ml). Thionyl chloride (2.0 ml, 27.4 mmol) was added and the mixture was vigorously refluxed for 2 h. After cooling, the solution was diluted with CH_3CN (20 ml) and ruthenium trichloride hydrate (150 mg, 0.72 mmol) and $NaIO_4$ (4.7 g, 21.7 mmol) were added followed by water (30 ml). The mixture was stirred at room temperature for 1 h then diluted with ether (400 ml). The water layer was extracted with ether (2×50 ml). The combined organic layers were washed with water (30 ml), satd aq sodium bicarbonate (30 ml) and brine (30 ml) and dried. Evaporation and chromatography (7:3 petrol and ether) gave (4*S*,5*R*)-5-[9-(2,2-dimethylpropionyloxy)nonyl]-2,2-dioxo-2λ^6-[1,3,2]-dioxathiolane-4-carboxylic acid methyl ester (**9**, 5.5 g, 93%) as an oil; δ_H: 5.0–4.8 (2H, m, C*H*OSO_2OCH, including br d, 4.88, $J=7.2$ Hz), 4.02 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.87 (3H, s, OCH_3), 2.0–1.9 (2H, m), 1.65–1.4 (4H, m), 1.4–1.2 (10H, m), 1.17 (9H, s, $(CH_3)_3$); δ_C: 178.51 (*C*=O), 165.25 (C=O), 84.05 (*C*HOCO), 79.76 (*C*HOCO), 64.25 (CH_2OCO), 53.57 (OCH_3), 38.61 ($C(CH_3)_3$), 32.84 (CH_2), 29.14 (CH_2), 29.01 (CH_2), 28.98 (CH_2), 28.69 (CH_2), 28.46 (CH_2), 27.09 ($C(CH_3)_3$), 25.73 (CH_2), 24.66 (CH_2); ν_{max}/cm^{-1}: 2932, 2858, 1775, 1725, 1399, 1287, 1211, 1160, 1034; $[\alpha]_D^{19}$ +33.7 (*c* 1.3, $CHCl_3$) (Found $(M+H)^+$: 409.1889; $C_{18}H_{33}O_8S$ requires: 409.1891).

3.1.5. (*R*)-12-(2,2-Dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (10). The cyclic sulfate (**9**, 2.04 g, 5 mmol) was dissolved in *N*,*N*-dimethylacetamide (25 ml) and $NaBH_4$ (190 mg, 5 mmol) was slowly added at 0 °C, stirred at 25 °C for 1 h, then concentrated by distillation under high vacuum. Ether (25 ml) and 10% aq H_2SO_4 (25 ml) were slowly added to the residue and stirred vigorously for 8 h. The water layer was extracted with ether (4×75 ml). The combined organic layers were washed with water and brine, dried and concentrated. Chromatography (7:3 petrol and ether) gave (*R*)-12-(2,2-dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (**10**, 900 mg, 55%) as an oil; δ_H: 4.00 (2H, t, $J=6.7$ Hz, CH_2OCO), 3.96 (1H, m, C*H*OH), 3.67 (3H, s, $COOCH_3$), 3.1–2.9 (1H, br s, O*H*), 2.47 (1H, dd, $J_1=16.1$ Hz, $J_2=3.2$ Hz, $COCH_2CHOH$), 2.38 (1H, dd, $J_1=16.1$ Hz, $J_2=9.1$ Hz, $COCH_2CHOH$), 1.65–1.55 (2H, m), 1.55–1.35 (3H, m), 1.4–1.2 (11H, m) 1.15 (9H, s, $(CH_3)_3$); δ_C: 178.58 (*C*=O), 173.36 (*C*=O), 67.92 (*C*HOH), 64.36 (CH_2OCO), 51.62 (OCH_3), 41.10 ($CHOHCH_2CO$), 38.63 ($C(CH_3)_3$), 36.46 (CH_2), 30.22 (CH_2), 29.37 (CH_2), 29.35 (CH_2), 29.32 (CH_2), 29.09 (CH_2), 28.50 (CH_2), 27.11 ($C(CH_3)_3$), 25.79 (CH_2), 25.36 (CH_2); ν_{max}/cm^{-1}: 3509, 2930, 2856, 1729, 1725, 1286, 1160; $[\alpha]_D^{19}$ −11.6 (*c* 1.1 in $CHCl_3$) (lit. $[\alpha]_D^{20}$ −13.8 (*c* 1.48 in $CHCl_3$) for (*R*)-3-hydroxyhexadecanoic acid methyl ester)[34] (Found $(M+H)^+$: 331.2472; $C_{18}H_{35}O_5$ requires: 331.2479).

3.1.6. (2*R*,3*R*)-2-Allyl-12-(2,2-dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (11). The ester (**10**, 330 mg, 1 mmol) in THF (5 ml) was added to a stirred solution of LDA (2.3 ml, 2.5 mmol, 1.1 M in hexanes) in THF (5 ml) at −55 °C. The temperature was slowly increased to −15 °C for 3.5 h, then reduced to −25 °C and 1-iodopropene (252 mg; 1.5 mmol) and HMPA (360 mg; 2 mmol) in THF (6 ml) was added dropwise at below −20 ° C, stirred at room temperature for 18 h, then

quenched with satd aq ammonium chloride (10 ml) and extracted with dichloromethane (3×25 ml). The combined organic layers were washed with water (10 ml), dried and evaporated. Chromatography (9:1 petrol and ethyl acetate) gave (2*R*,3*R*)-2-allyl-12-(2,2-dimethylpropionyloxy)-3-hydroxydodecanoic acid methyl ester (**11**, 230 mg; 62%)[27] as an oil, which showed δ_H: 5.72 (1H, m, C*H*=CH$_2$), 5.05 (2H, m, CH=C*H*$_2$), 4.03 (2H, t, J=6.6 Hz, C*H*$_2$OCO), 3.69 (4H, m, including s for COOC*H*$_3$), 2.6–2.5 (2H, m), 2.5–2.4 (2H, m), 1.4–1.2 (16H, m) 1.18 (9H, s, (C*H*$_3$)$_3$); δ_C: 178.44 (*C*=O), 175.10 (*C*=O), 134.85 (*C*H$_2$=CH), 116.93 (CH$_2$=*C*H), 71.61 (*C*HOH), 64.28 (*C*H$_2$OCO), 51.36 (O*C*H$_3$), 50.59 (CHOH*C*HCO), 38.58 (*C*(CH$_3$)$_3$), 35.32 (*C*H$_2$), 33.56 (*C*H$_2$), 29.34 (*C*H$_2$), 29.31 (*C*H$_2$), 29.28 (*C*H$_2$), 29.05 (*C*H$_2$), 28.47 (*C*H$_2$), 27.07 (C(*C*H$_3$)$_3$), 25.76 (*C*H$_2$), 25.56 (*C*H$_2$); ν_{max}/cm^{-1}: 3518, 2929, 2855, 1728, 1642, 1285, 1162; $[\alpha]_D^{19}$ +3.1 (*c* 1.1 in CHCl$_3$) (lit. $[\alpha]_D^{19}$ −11.5 (*c* 3.3 in CHCl$_3$) for (2*S*,3*S*)-2-allyl-3-hydroxypentanedioic acid dimethyl ester)[35] (Found (M+K)$^+$: 409.2368; $C_{21}H_{38}KO_5$ requires: 409.2351).

3.1.7. (2*R*,3*R*)-2-Allyl-3-(*tert*-butyldimethylsilanyloxy)-12-(2,2-dimethylpropionyloxy)dodecanoic acid methyl ester (12). Imidazole (465 mg, 6.8 mmol) was added to the alcohol (**11**, 1 g; 2.7 mmol) in dry DMF (9 ml), followed by *tert*-butyldimethylsilylchloride (530 mg, 3.5 mmol), then stirred at 40 °C overnight, when TLC showed no starting material. After concentrating, water was added and the product was extracted with dichloromethane (3× 50 ml). The combined organic layers were washed with water (2×15 ml), dried and evaporated. Chromatography eluting with 9:1 petrol and ether gave (2*R*,3*R*)-2-allyl-3-(*tert*-butyldimethylsilanyloxy)-12-(2,2-dimethylpropionyloxy)dodecanoic acid methyl ester (**12**, 1.1 g, 84%) as an oil; δ_H: 5.72 (1H, ddt, J_1=17.0 Hz, J_2=10.0 Hz, J_3=7.0 Hz, C*H*=CH$_2$), 5.03 (1H, dd, J_1=17.0 Hz, J_2=1.6 Hz, CH=C*H*$_2$), 4.98 (1H, m, CH=C*H*$_2$), 4.04 (2H, t, J=6.6 Hz, C*H*$_2$OCO), 3.93 (1H, m, C*H*OSi), 3.65 (3H, s, COOC*H*$_3$), 2.61 (1H, m, CHOH*C*HCO), 2.37 (2H, m, C*H*$_2$CH=CH$_2$), 1.7–1.2 (16H, m), 1.19 (9H, s, (COC*H*$_3$)$_3$), 0.87 (9H, s, (CC*H*$_3$)$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.03 (3H, s, SiC*H*$_3$); δ_C: 178.60 (*C*=O), 175.02 (*C*=O), 135.95 (*C*H$_2$=CH), 116.29 (CH$_2$=*C*H), 72.78 (*C*HOSi), 64.40 (*C*H$_2$OCO), 51.35 (*C*HCO), 51.26 (O*C*H$_3$), 38.71 (*C*(CH$_3$)$_3$), 33.64 (*C*H$_2$), 31.57 (*C*H$_2$), 29.70 (*C*H$_2$), 29.43 (*C*H$_2$), 29.41 (*C*H$_2$), 29.18 (*C*H$_2$), 28.61 (*C*H$_2$), 27.19 (C(*C*H$_3$)$_3$), 25.81 (C(*C*H$_3$)$_3$), 25.73 (*C*H$_2$), 25.68 (*C*H$_2$), 24.13 (*C*H$_2$), 17.97 (Si*C*(CH$_3$)$_3$), −4.41 (Si*C*H$_3$), −4.90 (Si*C*H$_3$); ν_{max}/cm^{-1}: 3078, 2929, 2856, 1731, 1642, 1156; $[\alpha]_D^{20}$ −13.3 (*c* 1.3 in CHCl$_3$) (Found (M+K)$^+$: 523.3229; $C_{27}H_{52}KO_5Si$ requires: 523.3216).

3.1.8. 5-Docosylsulfanyl-1-phenyl-1*H*-tetrazole (22). Potassium carbonate (3 g, 21.2 mmol) was added to a solution of 1-bromodocosane (**14**, 5.5 g, 14.1 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (2.6 g, 14.8 mmol) in acetone (500 ml). The mixture was vigorously stirred and refluxed at 60 °C overnight. The solvent was evaporated and the residue was dissolved in water (300 ml) and extracted with dichloromethane (3×300 ml). The combined organic layers were dried and evaporated. Recrystallisation from acetone (100 ml) and methanol (200 ml) gave 5-docosylsulfanyl-1-phenyl-1*H*-tetrazole (**22**, 6.5 g, 96%) as a colourless solid, mp 70–72 °C, which showed δ_H: 7.55–7.45 (5H, m, aromatic), 3.40 (2H, t, J=7.2 Hz, C*H*$_2$S), 1.82 (2H, m), 1.6 (4H, m), 1.45 (2H, m), 1.35–1.25 (32H, br m), 0.89 (3H, t, J=6.6 Hz, C*H*$_3$); δ_C: 154.33 (C=N heterocyclic), 133.79 (C–N aromatic), 130.05 (CH aromatic), 129.75 (CH aromatic), 123.87 (CH aromatic), 33.40 (*C*H$_2$S), 31.92 (*C*H$_2$), 29.69 (*C*H$_2$), 29.65 (*C*H$_2$), 29.61 (*C*H$_2$), 29.54 (*C*H$_2$), 29.43 (*C*H$_2$), 29.35 (*C*H$_2$), 29.08 (*C*H$_2$), 29.02 (*C*H$_2$), 28.64 (*C*H$_2$), 22.68 (*C*H$_2$), 14.10 (*C*H$_3$); ν_{max}/cm^{-1}; 3017, 2925, 2853, 1598, 1500 (Found (M+H)$^+$: 487.3837; $C_{29}H_{51}N_4S^+$ requires: 487.3829).

3.1.9. 5-(Docosane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (15). Ammonium molybdate tetrahydrate (8 g, 0.70 mmol) was dissolved in stages in aq H_2O_2 (31 ml, 300 mmol, 35% w/w) and added slowly the sulfide (**22**, 6.2 g, 12.7 mmol) in IMS and THF (3:5, 400 ml). After stirring at room temperature for 2 h, ammonium molybdate tetrahydrate (8 g, 0.70 mmol) in aq H_2O_2 (31 ml, 300 mmol, 35% w/w) was added and stirred overnight. After partial concentration, the reaction was quenched with water (150 ml) and extracted with dichloromethane (3×150 ml). The combined organic layers were dried and evaporated. Chromatography eluting with 8:1 petrol and ether gave 5-(docosane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**15**, 6.1 g, 93%) as a colourless solid, mp 56–59 °C, which showed δ_H: 7.70 (2H, m, aromatic), 7.61 (3H, m, aromatic), 3.72 (2H, m, C*H*$_2$S), 1.95 (2H, m, C*H*$_2$CH$_2$S), 1.50 (2H, m), 1.4–1.2 (36H, m), 0.89 (3H, t, J=7.2 Hz, C*H*$_3$); δ_C: 153.50 (C=N heterocyclic), 133.06 (C–N aromatic), 131.39 (CH aromatic), 129.67 (CH aromatic), 125.06 (CH aromatic), 56.01 (*C*H$_2$S), 31.90 (*C*H$_2$), 29.68 (*C*H$_2$), 29.64 (*C*H$_2$), 29.61 (*C*H$_2$), 29.54 (*C*H$_2$), 29.44 (*C*H$_2$), 29.33 (*C*H$_2$), 29.17 (*C*H$_2$), 28.87 (*C*H$_2$), 28.12 (*C*H$_2$), 22.667 (*C*H$_2$), 21.91 (*C*H$_2$), 14.08 (*C*H$_3$); ν_{max}/cm^{-1}: 3018, 2926, 2854, 1498, 1342, 1152 (Found (M+H)$^+$: 519.3706; $C_{29}H_{51}N_4O_2S$ requires: 519.3727).

3.1.10. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)decyl]-hexacos-4-enoic acid methyl ester (16). To a solution of alkene (**12**, 150 mg, 0.3 mmol) in dioxane–water (3/1, 8 ml) were added 2,6-lutidine (66 mg, 0.6 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 62 mg, 75 μl, 0.006 mmol), and $NaIO_4$ (260 mg, 1.2 mmol). After 2 h stirring at 25 °C, the reaction was complete by TLC; water (10 ml) and dichloromethane (20 ml) were added. The water layer was extracted by dichloromethane (3×10 ml). The combined organic layers were washed with brine (10 ml), dried and concentrated. Chromatography eluting with 9:1 ether/ petrol gave (2*R*,3*R*)-3-(*tert*-butyldimethylsilanyloxy)-12-(2,2-dimethylpropionyloxy)-2-(2-oxoethyl)dodecanoic acid methyl ester (**13**, 130 mg, 92%) as a colourless oil, which was immediately used without complete characterization (δ_H: 9.79 (1H, m, C*H*=O), 4.05–4.00 (3H, including 4.02, t, J=6.7 Hz, C*H*$_2$OCO), 3.65 (3H, s, COOC*H*$_3$), 3.18 (1H, dt, J_1=10.4 Hz, J_2=3.7 Hz, *C*HCO), 2.94 (1H, dd, J_1=18 Hz, J_2=10.4 Hz, C*H*$_2$CH=O), 2.65 (1H, dd, J_1=18 Hz, J_2=3.4 Hz, C*H*$_2$CH=O), 1.7–1.2 (16H, m), 1.17 (9H, s, (COC*H*$_3$)$_3$), 0.85 (9H, s, (CC*H*$_3$)$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.04 (3H, s, SiC*H*$_3$)).

Lithium bis(trimethylsilyl)amide (0.4 mmol, 0.4 ml, 1 M, in hexanes) was added at −10 °C to a solution of the aldehyde

(**13**, 130 mg, 0.28 mmol) and the sulfone (**14**, 180 mg, 0.36 mmol) in dry THF (10 ml) under nitrogen. The reaction was stirred at room temperature for 24 h then quenched with satd aq ammonium chloride (10 ml) and extracted with dichloromethane (3×40 ml). The combined organic layers were dried and concentrated. Chromatography eluting with 10:0.5 petrol and ether gave (*E*,*Z*)-(*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)-decyl]hexacos-4-enoic acid methyl ester ((*E*)/(*Z*), 2.7:1) (**16**, 185 mg, 85%) as an oil, which showed δ_H: 5.42 (1H, m, C*H*=CH), 5.30 (1H, m, C*H*=CH), 4.04 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.92 (1H, m, C*H*OSi), 3.64 (3H, s, OCH_3), 2.57 (1H, m, *C*HCO), 2.4–2.1 (2H, m), 2.1–1.9 (2H, m), 1.8–1.6 (2H, m), 1.8–1.3 (55H, m), 1.19 (9H, s, (COCH_3)$_3$), 0.87 (9H, s, (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 178.68 (*C*=O), 174.44 (*C*=O, Z), 174.37 (*C*=O, E), 132.80 (*C*H=CH, E), 131.92 (*C*H=CH, Z), 126.88 (CH=*C*H, E), 126.25 (*C*H=CH, Z), 72.96 (*C*HOSi, Z), 72.83 (*C*HOSi, E), 64.46 (*C*H_2OCO), 51.85 (*C*HCO, E), 51.75 (*C*HCO, Z), 51.32 (O*C*H$_3$, Z), 51.21 (O*C*H$_3$, E), 38.74 (*C*(CH$_3$)$_3$), 33.69 (*C*H$_2$), 32.55 (*C*H$_2$), 31.94 (*C*H$_2$), 30.71 (*C*H$_2$), 29.72 (*C*H$_2$), 29.67 (*C*H$_2$), 29.55 (*C*H$_2$), 29.51 (*C*H$_2$), 29.50 (*C*H$_2$), 29.47 (*C*H$_2$), 29.38 (*C*H$_2$), 29.23 (*C*H$_2$), 29.12 (*C*H$_2$), 27.22 (C(*C*H$_3$)$_3$), 25.91 (*C*H$_2$), 25.75 (C(*C*H$_3$)$_3$), 23.92 (*C*H$_2$), 22.69 (*C*H$_2$), 17.98 (Si*C*(CH$_3$)$_3$), 14.11 (*C*H$_3$), −4.38 (Si*C*H$_3$), −4.91 (Si*C*H$_3$); ν_{max}/cm^{-1}: 2922, 2853, 1732, 1464, 1157; $[\alpha]_D^{20}$ −5.9 (*c* 1.1 in CHCl$_3$) (Found (M+K)$^+$: 817.6502; $C_{48}H_{94}KO_5Si$ requires: 817.6502).

3.1.11. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)-decyl]-hexacosanoic acid methyl ester (17). The alkene (**16**, 550 mg, 0.7 mmol) was dissolved IMS and ethyl acetate (1:3, 32 ml) then Pd on C (10%, 100 mg) was added. The mixture was stirred under hydrogen, until no more was absorbed, then diluted with diethyl ether (150 ml) and filtered on a pad of Celite. The filtrate was evaporated; chromatography eluting with petrol and ether (9:1) gave (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-(2,2-dimethylpropionyloxy)decyl]hexacosanoic acid methyl ester (**17**, 520 mg, 95%) as an oil, which showed δ_H: 4.05 (2H, t, $J=6.6$ Hz, CH_2OCO), 3.90 (1H, m, C*H*OSi), 3.66 (3H, s, OCH_3), 2.53 (1H, ddd, $J_1=11$ Hz, $J_2=7.0$ Hz, $J_3=3.5$ Hz, *C*HCO), 1.6–1.2 (62H, m), 1.21 (9H, s, (COCH_3)$_3$), 0.87 (12H, m, CH_3, and (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 178.64 (*C*=O), 174.10 (*C*=O), 73.20 (*C*HOSi), 64.44 (*C*H$_2$OCO), 51.60 (*C*HCO), 51.21 (O*C*H$_3$), 38.72 (*C*(CH$_3$)$_3$), 33.67 (*C*H$_2$), 31.92 (*C*H$_2$), 29.80 (*C*H$_2$), 29.70 (*C*H$_2$), 29.65 (*C*H$_2$), 29.58 (*C*H$_2$), 29.48 (*C*H$_2$), 29.45 (*C*H$_2$), 29.35 (*C*H$_2$), 29.20 (*C*H$_2$), 29.05 (*C*H$_2$), 28.61 (*C*H$_2$), 27.85 (*C*H$_2$), 27.65 (*C*H$_2$), 27.21 (C(*C*H$_3$)$_3$), 25.91 (*C*H$_2$), 25.76 (C(*C*H$_3$)$_3$), 23.92 (*C*H$_2$), 22.69 (*C*H$_2$), 17.98 (Si*C*(CH$_3$)$_3$), 14.11 (*C*H$_3$), −4.38 (Si*C*H$_3$), −4.93 (Si*C*H$_3$); ν_{max}/cm^{-1}: 2923, 2852, 1732, 1458, 1155; $[\alpha]_D^{23}$ −4.7 (*c* 1.1 in CHCl$_3$) (lit. $[\alpha]_D^{20}$ −35.1 (*c* 1.34 in CHCl$_3$) for methyl (3*R*)-*tert*-butyldimethylsilyloxy-(2*R*)-methylpentanoate)[36] (Found (M+K)$^+$: 819.6649; $C_{48}H_{96}KO_5Si$ requires: 819.6659).

3.1.12. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-hydroxydecyl]hexacosanoic acid methyl ester (23). The pivaloyl-protected alcohol (**17**, 200 mg, 0.26 mmol) was added to potassium hydroxide (215 mg, 3.8 mmol) in THF, MeOH and H_2O (21 ml, 10:10:1). The mixture was refluxed at 70 °C and monitored by TLC. After 4 h, TLC showed no starting material and the reaction was quenched with water and extracted with ethyl acetate (3×100 ml), dried and concentrated. Chromatography eluting with 1:1 petrol and ether gave (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-hydroxydecyl]hexacosanoic acid methyl ester (**23**, 170 mg, 94%) as an oil, which showed δ_H: 3.90 (1H, m, C*H*OSi), 3.66 (5H, m, HOCH_2 and OCH_3), 2.53 (1H, ddd, $J_1=10.7$ Hz, $J_2=7.0$ Hz, $J_3=3.8$ Hz, *C*HCO), 1.6–1.2 (63H, m), 0.88 (12H, m, CH_3, and (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 175.18 (*C*=O), 73.25 (*C*HOSi), 63.09 (*C*H$_2$OH), 51.66 (*C*HCO), 51.18 (O*C*H$_3$), 33.73 (*C*H$_2$), 32.83 (*C*H$_2$), 31.92 (*C*H$_2$), 29.81 (*C*H$_2$), 29.70 (*C*H$_2$), 29.65 (*C*H$_2$), 29.58 (*C*H$_2$), 29.52 (*C*H$_2$), 29.49 (*C*H$_2$), 29.45 (*C*H$_2$), 29.39 (*C*H$_2$), 29.35 (*C*H$_2$), 27.86 (*C*H$_2$), 27.47 (*C*H$_2$), 25.78 (C(*C*H$_3$)$_3$), 23.87 (*C*H$_2$), 22.67 (*C*H$_2$), 22.67 (*C*H$_2$), 17.99 (Si*C*(CH$_3$)$_3$), 14.07 (*C*H$_3$), −4.37 (Si*C*H$_3$), −4.90 (Si*C*H$_3$). ν_{max}/cm^{-1}: 3358, 2923, 2859, 1738, 1465; $[\alpha]_D^{22}$ −4.0 (*c* 1.2 in CHCl$_3$) (Found (M+H)$^+$: 697.6542; $C_{43}H_{89}O_4Si$ requires: 697.6525).

3.1.13. (*R*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-10-oxodecyl]hexacosanoic acid methyl ester (3). The alcohol (**23**, 100 mg, 0.14 mmol) in dichloromethane (5 ml) was added to PCC (80 mg, 0.36 mmol) in dichloromethane (30 ml). The mixture was vigorously stirred for 2 h when TLC showed no starting material, then diluted with ether (50 ml) and filtered on a pad of Celite and silica. The solvent was evaporated; chromatography (1:1 petrol/ether) gave (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-10-oxo-decyl]-hexacosanoic acid methyl ester (**3**, 90 mg, 91%) as an oil, δ_H: 9.77 (1H, t, $J=1.9$ Hz, C*H*O), 3.9 (1H, m, C*H*OSi), 3.66 (3H, s, OCH_3), 2.53 (1H, ddd, $J_1=10.9$ Hz, $J_2=7.0$ Hz, $J_3=3.8$ Hz, *C*HCO), 2.39 (2H, br dt, $J_1=7.5$ Hz, $J_2=1.9$ Hz, CH_2CHO), 1.7–1.2 (60H, m), 0.88 (12H, m, CH_3, and (CCH_3)$_3$), 0.05 (3H, s, SiCH_3), 0.03 (3H, s, SiCH_3); δ_C: 202.64 (*C*H=O), 175.00 (*C*=O), 73.23 (*C*HOSi), 51.65 (*C*HCO), 51.17 (O*C*H$_3$), 43.89 (*C*H$_2$CH=O), 33.71 (*C*H$_2$), 31.92 (*C*H$_2$), 29.75 (*C*H$_2$), 29.69 (*C*H$_2$), 29.65 (*C*H$_2$), 29.58 (*C*H$_2$), 29.44 (*C*H$_2$), 29.34 (*C*H$_2$), 29.28 (*C*H$_2$), 29.14 (*C*H$_2$), 27.86 (*C*H$_2$), 27.46 (*C*H$_2$), 25.76 (C(*C*H$_3$)$_3$), 23.85 (*C*H$_2$), 22.67 (*C*H$_2$), 22.10 (*C*H$_2$), 17.98 (Si*C*(CH$_3$)$_3$), 14.07 (*C*H$_3$), −4.38 (Si*C*H$_3$), −4.90 (Si*C*H$_3$). ν_{max}/cm^{-1}: 2924, 2953, 2710, 1738, 1464; $[\alpha]_D^{25}$ −6.4 (*c* 1.4 in CHCl$_3$) (Found (M+H)$^+$: 695.63651; $C_{43}H_{87}O_4Si$ requires: 695.63681).

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27. In the case of the homologue of (**10**) with 10 instead of nine methylene groups in the chain good yields were only achieved if the reaction was carried out as follows: Butyllithium (13.33 ml, 28 mmol, 2.1 M) was added to a stirred solution of diisopropylamine (3.73 ml, 26.66 mmol) in dry THF (120 ml) at −78 °C under argon. The mixture was allowed to reach room temperature and stirred for 15 min. It was then cooled to −78 °C and the ester (4.17 g, 12.12 mmol) in dry THF (45 ml) was added. The mixture was allowed to warm to −5 °C over 2 h, stirred at 0–2 °C for 0.5 h, then cooled to −70 °C and 1-iodoprop-2-ene (1.55 ml, 17.0 mmol) and HMPA (6.32 ml, 36.4 mmol) in dry THF (10 ml) were added. The reaction was allowed to reach 0 °C over 1.5 h and then quenched with aq ammonium chloride (10 ml) followed by brine (100 ml). The product was extracted with petrol–ethyl acetate (1/1, 3× 100 ml). The combined organic layers were washed with water, dried and evaporated to give a pale yellow oil. Column chromatography eluting with 5:2 petrol and ethyl acetate gave the product as a colourless oil (2.56 g, 56%) (Al-Dulayymi, J. R. and Koza, G. Unpublished results).
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