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The synthesis of single enantiomers of mycobacterial ketomycolic acids containing *cis*-cyclopropanes

Gani Koza, Cornelia Theunissen, Juma'a R. Al Dulayymi, Mark S. Baird *

School of Chemistry, Bangor University, Bangor, Gwynedd LL 57 2 UW, UK

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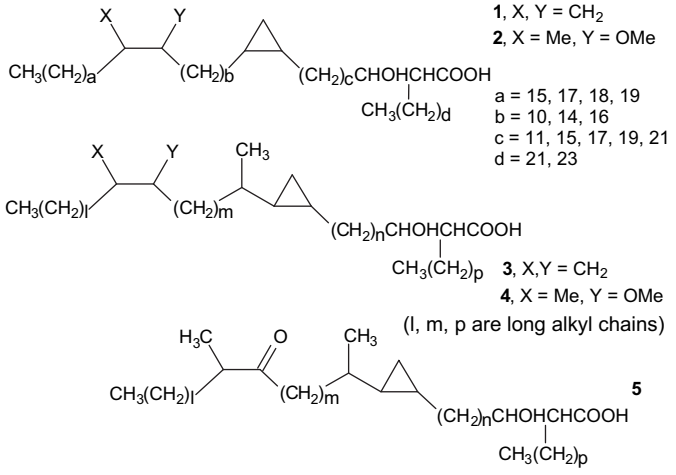
ABSTRACT

We report the syntheses of a single enantiomer of an unprotected ketomycolic acids containing a *cis*-cyclopropane and of related hydroxy-mycolic acids.

1. Introduction

Mycolic acids (MAs), eg. **1**–**5** (Scheme 1), are major constituents of the cell envelope of *Mycobacterium tuberculosis* and other mycobacteria, some of which are pathogenic to animals and humans.[1–4] Their presence is thought to be linked to the resistance of these organisms to many antibiotics and other chemo-therapeutic agents.[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.[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.[11,12] 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 anti-tumour properties of MA derivatives.[14] There is evidence that the methoxy and methyl groups of MAs **2** and **4** are *S*,*S* and that the α-methylketone of ketomycolates is *S*, though it is not clear whether the stereochemistry is important for biological effect.[7,15] The balance of α-MAs **1** and **3**, methoxy- **2** and **4** and keto-MAs such as **5** is characteristic of specific bacteria;[4,5] in each case, each type of MA is present as a mixture of homologues. The chain lengths of MAs depend on the rate of growth of the bacterium.[16] In the case of the keto-MAs, the balance of those containing a *cis*-cyclopropane (**7**) and an α-methyl-*trans*-cyclopropane (**6**) is highly dependent on the mycobacterial strain; thus for *M. tuberculosis* Aoyama B the ratio is 1:3.3 whereas for *M. tuberculosis* H37Ra it is 1:0.03.[4] In the case of *M. tuberculosis*, the exact role of each type in the pathogenesis of disease remains to be confirmed, but the oxygenated MAs have a particular influence on macrophage growth; strains lacking ketomycolates have a reduced ability to grow within THP-1 cells.[17] Moreover, the absence of keto and methoxymycolates leads to attenuation of *M. tuberculosis* in mice; the vaccine strain *Mycobacterium bovis* BCG-Pasteur lacks methoxy-mycolates.[18] Moreover cyclopropane stereochemistry plays a key role in pathogenesis and immuno-modulatory function; thus a mutant strain lacking the ability to produce *trans*-cyclopropanes enhances the induced macrophage inflammatory response.[19] The stereochemistry was

* Corresponding author.
E-mail address: m.baird@bangor.ac.uk (M.S. Baird).

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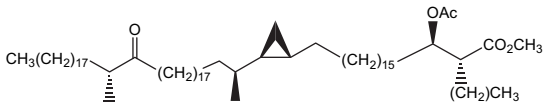
shown to affect host innate immune responses both positively and negatively. We have recently reported the synthesis of an α-mycolate of type **1**,[20,21] and of methoxymycolates of type **2** with either absolute stereochemistry at the *cis*-cyclopropane or α-methyl-β-methoxy fragment.[22] We have also reported the synthesis of meromycolate fragments containing the α-methyl-*trans*-cyclopropane unit and provided evidence that the relative stereochemistry of methyl and cyclopropane is as shown in **6**, and that, at least in the case of wax esters derived by enzymatic Baeyer–Villiger reaction of keto-mycolates, the absolute stereochemistry of this sub-unit is also as shown in **6**.[23] If **6** and **7** are produced through a common intermediate derived by adding a methyl group from SAM to a *cis*-alkene, the stereochemistry of the *cis*-cyclopropane can then be inferred to be as shown in **7**. We have briefly reported syntheses of protected ketomycolates containing both α-methyl-*trans*- and *cis*-cyclopropane fragments, **6** and **7**, that can be adjusted to produce a variety of absolute stereochemistries and chain lengths. However, deprotection of these led to epimerisation at the methyl-position adjacent to the ketone.[24]

2. Results and discussion

We now report in full the synthesis of the three stereoisomers of the *cis*-ketomycolic acid **7**, having chain lengths matching those of a significant component in many mycobacteria,[4] and the deprotection of one of these to give a single enantiomer of free mycolic acid with *S*-stereochemistry adjacent to the ketone (Scheme 2).



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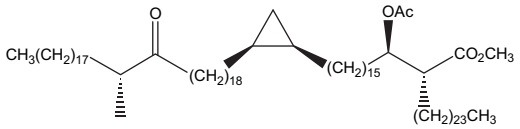
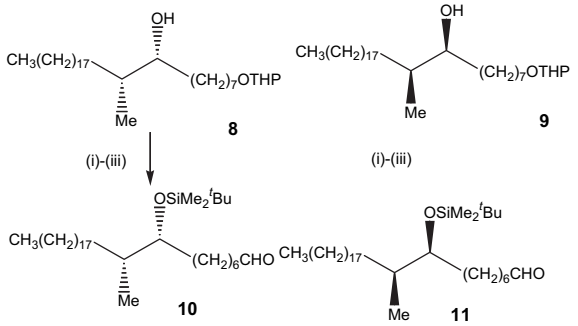


7

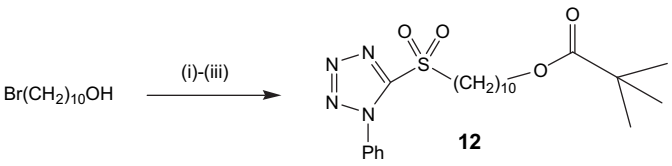
Scheme 2.

The α-methylketone was introduced through either **8**[22] or its enantiomer, **9**.[22] Protection of the secondary alcohol, deprotection of the primary alcohol and then oxidation led to the two aldehydes, **10** and **11** (Scheme 3).

The sulfone **12** was prepared from 10-bromodecan-1-ol by reaction with trimethylacetyl chloride, followed by 1-phenyl-1*H*-tetrazole-5-thiol to give the corresponding thiane and then oxidation (Scheme 4).

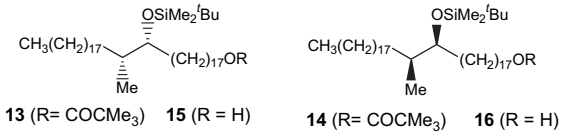


Scheme 3. (i) Imidazole, DMF, then TBDMSCl, rt, 18 h then 50 °C, 5 h (84,88%); (ii) pyridinium-*p*-toluenesulfonate, MeOH, THF (86, 94%); (iii) PCC, CH_2Cl_2 (97,97%) (first% refers to 8–10, second to 9–11).



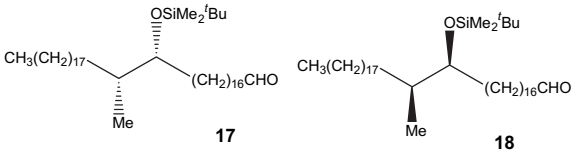
Scheme 4. (i) Trimethylacetyl chloride, pyridine, DMAP, rt, 18 h (85%); (ii) 1-phenyl-1*H*-tetrazole-5-thiol, potassium carbonate, acetone, 18 h, rt (93%); (iii) ammonium molybdate (VI) tetrahydrate, H_2O_2, THF, IMS, rt, 20 h (97%).

Reaction of either **10** or **11** with sulfone **12** and base in a modified Julia-Kocienski reaction[25] led to a mixture of *E*/*Z*-alkenes which was hydrogenated to give the chain extended esters **13** and **14** (Scheme 5).



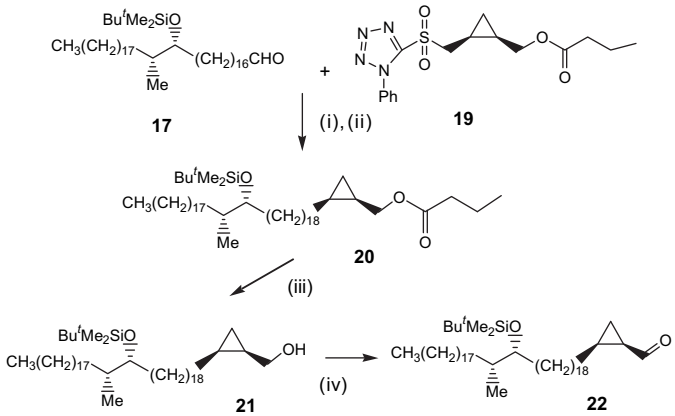
Scheme 5.

These were each deprotected by reductive removal of the ester group to give the corresponding alcohols **15** and **16** and then oxidised to the corresponding aldehyde, **17** or **18** (Scheme 6).



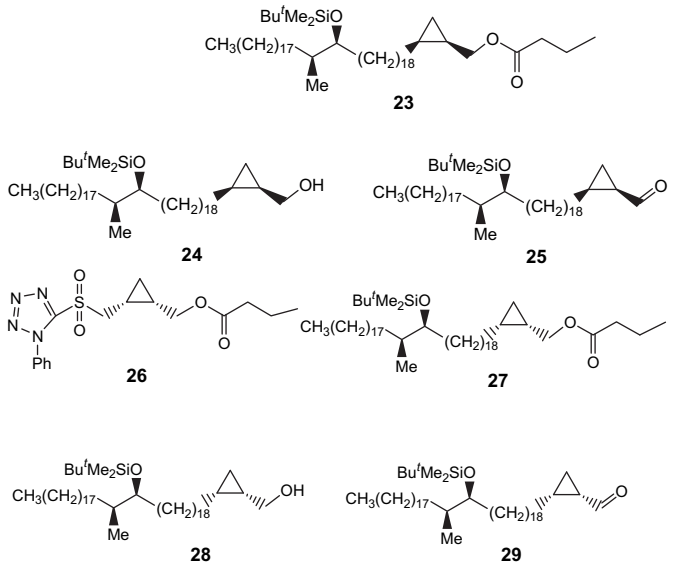
Scheme 6.

For the synthesis of stereoisomers of compound **7**, the *cis*-cyclopropane was introduced as **19**[21–23] or its enantiomer.[20–22] Condensation of **17** with **19** in a modified Julia-Kocienski reaction,[25] followed by saturation of the derived *E*/*Z* alkene mixture using diimide, led to ester **20**. Removal of the ester group reductively followed by oxidation of the derived alcohol **21**, led to aldehyde **22** (Scheme 7)



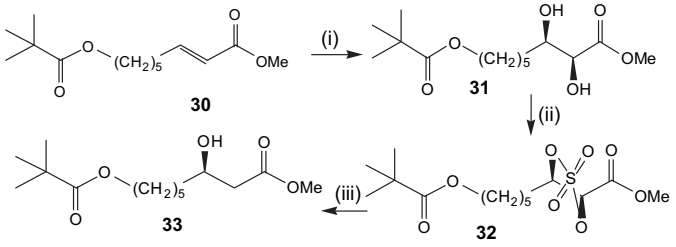
Scheme 7. (i) THF, LiN($SiMe_3$)$_2$, −12 and −5 °C; (ii) 2,4,6-tri-isopropylbenzenesulphonyl hydrazide, THF (70%, 2 steps); (iii) LAH, THF, 0 °C (97%); (iv) PCC, CH_2Cl_2, rt, 2 h (100%).

In the same way, **19** and the enantiomeric aldehyde **18** were converted into the ester **23** and hence the alcohol **24** and aldehyde **25**. The enantiomer of **19**, compound **26** was reacted in the same way with **18** to give eventually the aldehyde **29** via **27** and **28** (Scheme 8).



Scheme 8.

R,*R*-2-Alkyl-3-hydroxy acids have been prepared before by a number of methods including asymmetric reduction of the corresponding ketone either chemically or enzymically.[26–29] In this work it was introduced by two different methods, both based on alkylation of an *R*-3-hydroxy ester. In the first, already reported for a different chain length,[30] a cyclic sulfate **32** was prepared from the diol **31**, prepared by Sharpless asymmetric hydroxylation. The sulfate **32** was reduced to the alcohol and esterified to produce **33** (Scheme 9).

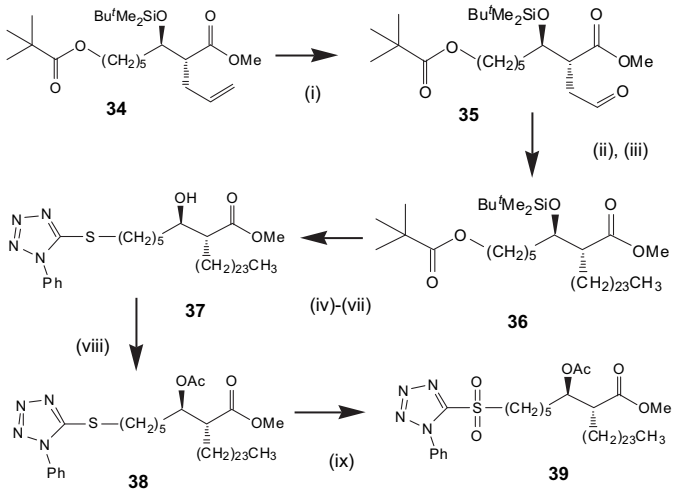


Scheme 9. (i) (DHQD)$_2$PHAL (1 mol %), $K_3Fe(CN)_6$ (3 mol equiv.), K_2CO_3 (3 mol equiv.), OsO_4 (4 mol %), $MeSO_2NH_2$ (1 mol equiv.), ^{t}BuOH, H_2O (96%); (ii) 1-$SOCl_2$, (2 mol equiv.), CCl_4, 2-$NaIO_4$ (1.5 mol equiv.), $RuCl_3 \cdot H_2O$, (5 mol %), in CCl_4, CH_3CN. H_2O (90%); (iii) $NaBH_4$ (1 mol equiv), *N*,*N*-Dimethylacetamide, then H_2SO_4, ether (78%).

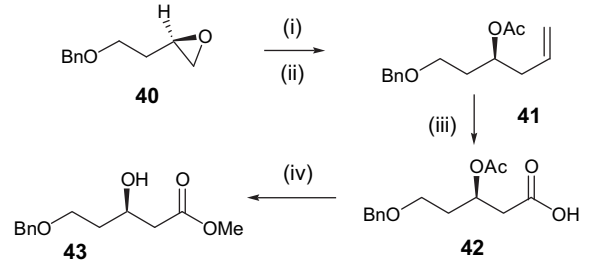
The ester **33** was allylated in a Frater reaction,[31] followed by silylation of the alcohol to produce **34**. This was then chain extended by a method that has previously been reported for a homologue to give diester **36** (see Supplementary information). The pivaloyl ester was removed and the alcohol produced converted into the corresponding bromide. Substitution of the bromine under standard conditions gave the corresponding thiane. The silyl protecting group was then exchanged for an acetate and the thiane oxidised to sulfone **39**. The Julia-Kocienski reaction of this leading to the complete keto-mycolic acid is described later (Scheme 10).

In the second approach to the enantiopure 3-hydroxyacid unit, ring opening of the epoxide **40**[32–35] with vinylmagnesium bromide followed by protection as the acetate gave **41**, which was oxidised and transformed to hydroxy-ester **43** (Scheme 11).

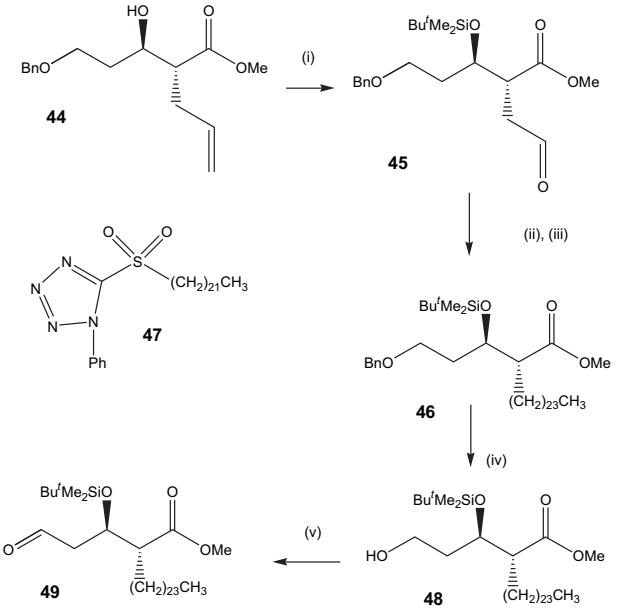
The hydroxy ester could then be allylated, again using the Frater method. Introduction of the allyl group to give **44**, then protection of the secondary alcohol followed by oxidative cleavage of the alkene as reported earlier for a homologue[30] led to an aldehyde **45**. This could be chain extended to **46** using the method reported (Scheme 12) earlier.[30]



Scheme 10. (i) 2,6-Lutidine, OsO_4 (2.5% in 2-methyl-2-propanol), then $NaIO_4$, 1,4-dioxane, H_2O, 25 °C, 2 h; (ii) $LiN(SiMe_3)_2$, 5-(docosane-1-sulfonyl)-1-phenyl-1*H*-tetrazole, THF, argon, rt, 2.5 h (83%); (iii) IMS, EtOAc, Pd/C, H_2 (98%); (iv) KOH, THF:MeOH:H_2O, 70 °C, 3 h (90%); (v) PPh_3, CH_2Cl_2, NBS, rt, 1.5 h (87%); (vi) 1-phenyl-1*H*-tetrazole-5-thiol, K_2CO_3, acetone, 18 h, rt (97%); (vii) THF, AcOH, water, 2 M HCl, rt, 18 h (75%); (viii) Ac_2O, pyridine, toluene, rt, 18 h (98%); (ix) ammonium molybdate, H_2O_2, THF, IMS, rt, 20 h (97%).

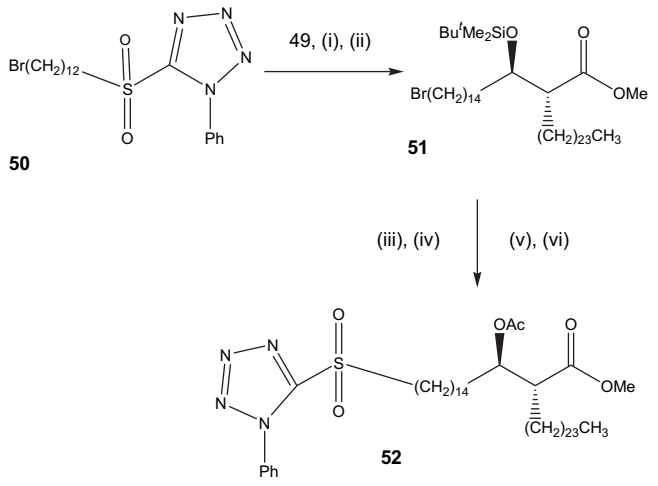


Scheme 11. (i) Copper iodide, THF, argon, vinylmagnesium bromide, −75 to −40 °C, −40 to −30 °C for 1 h, then −20 °C, 15 min; (ii) Ac_2O, pyridine, toluene, rt, 18 h (99%); (iii) DMF, oxone, OsO_4 (2.5% in 2-methyl-2-propanol), 32 °C, 3 h (78%); (iv) conc. H_2SO_4, MeOH, reflux, 3.5 h (78%).



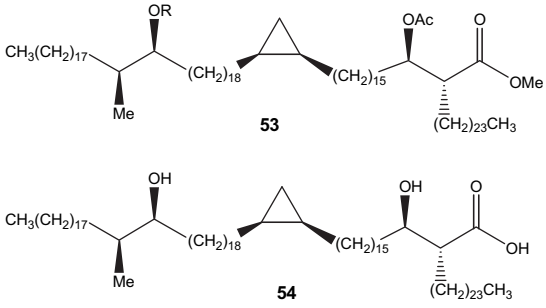
Scheme 12. (i) (a) imidazole, DMF, TBDMSCl (87%); (b) 2,6-Lutidine, OsO_4 (2.5% in 2-methyl-2-propanol), $NaIO_4$, 1,4-dioxane, water, 25 °C, 2 h; (ii) **47**, $LiN(SiMe_3)_2$, THF, rt, 3 h (83%); (iii) 10% Pd/C, THF/IMS, H_2, 1 h (98%); (iv) 10% Pd/C, EtOAc, H_2, 3 days (95%); (v) PCC, CH_2Cl_2, 2 h (90%).

The sulfone **50** was prepared from 12-bromo-dodecanol by standard methods. Compound **49** was subjected to a Julia-Kocienski reaction using **50**, followed by saturation of the derived *E*/*Z*-mixture of alkenes to give the bromide **51**. This was then converted into the corresponding sulfone **52**, again by standard methods (Scheme 13).



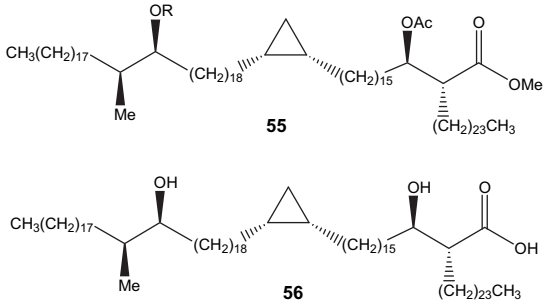
Scheme 13. ; (i) $LiN(SiMe_3)_2$, **49**, THF, rt 3 h (82%); (ii) H_2, Pd/C, IMS, THF (92%); (iii) 1-phenyl-1*H*-tetrazole-5-thiol, K_2CO_3, acetone (86%); (iv) HF.pyridine, pyridine, THF, 45 °C, 18 h (84%); (v) Ac_2O, pyridine, toluene, rt, 18 h (83%); (vi) MCPBA, CH_2Cl_2, rt, 18 h (82%).

A modified Julia-Kocienski reaction between the aldehyde **25** and sulfone **52**, followed by saturation of the *E*/*Z*-alkene mixture with diimide gave the protected hydroxymycolic acid **53** (R=$SiMe_2Bu^t$); the silyl protecting group was then removed to give **53** (R=H) (Scheme 14).



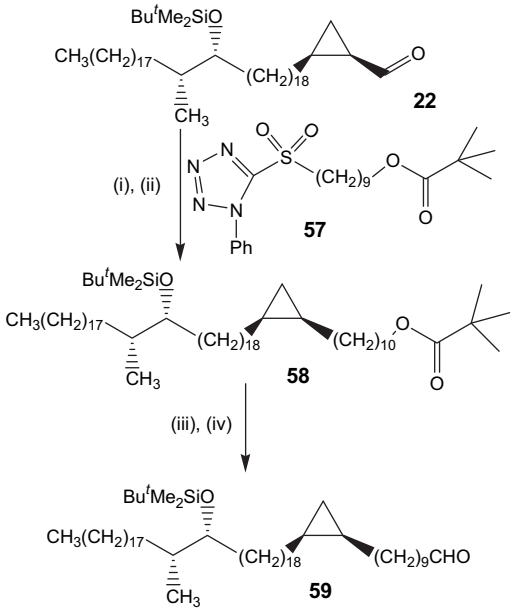
Scheme 14.

This was deprotected to produce the free hydroxymycolic acid **54**. In the same way the diastereoisomeric hydroxymycolic acid **56** was prepared from **29** and **52** via the protected species **55** (R=$SiMe_2Bu^t$) and **55** (R=H) (Scheme 15).



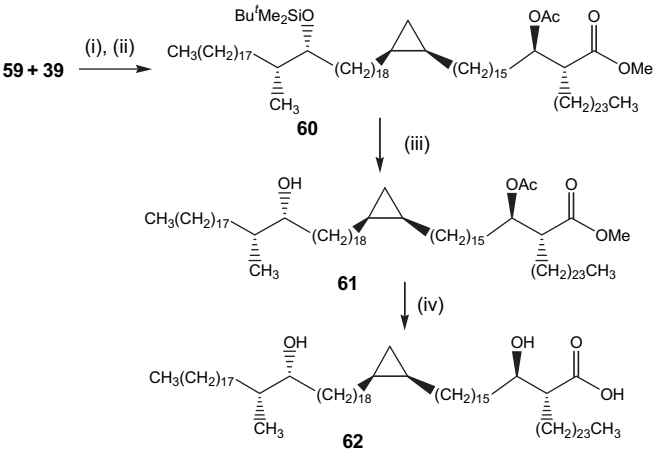
Scheme 15.

The *R*-methyl-*R*-hydroxy isomer **62** was prepared in a similar fashion from compound **22**, which was first converted into **58** via a Julia-Kocienski reaction with **57** (prepared in an analogous manner to **12**, see Supplementary information) as shown below (Scheme 16).



Scheme 16. (i) **57**, $LiN(SiMe_3)_2$, THF, rt, 3 h (87%); (ii) 2,4,6-Tri-isopropylbenzene-sulphonyl hydrazine (93%); (iii) $LiAlH_4$/THF (69%); (iv) PCC, CH_2Cl_2, rt, 2 h (95%).

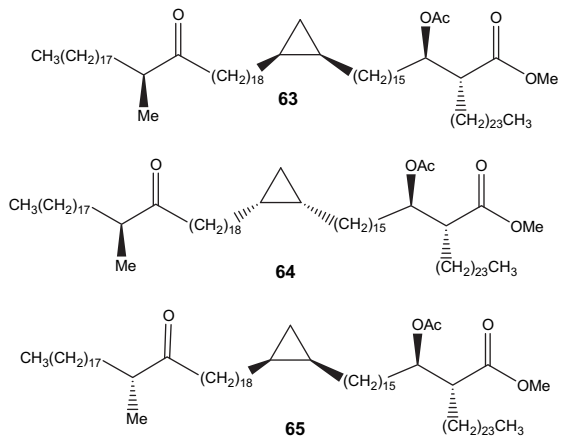
Compound **59** was then coupled with **39** and base followed by hydrogenation of the derived alkene to give **60**. Deprotection to **61** then led to the third isomer of hydroxymycolic acid **62** (Scheme 17).



Scheme 17. (i) THF, $LiN(SiMe_3)_2$, rt, 2 h (56%); dipotassium azodicarb-oxylate, THF, MeOH, AcOH (2.5 ml), rt, 2 h (88%); (iii) HF.pyridine, 17 h, 40 °C (94%); (iv) LiOH, THF, MeOH, H_2O, 45 °C, 18 h (61%).

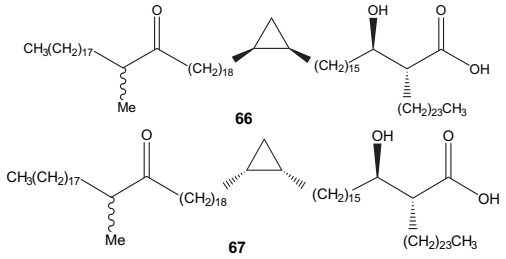
Although hydroxymycolic acids are not among the most common MAs that have been reported, there is increasing evidence for their importance. They are thought to be on the bio-synthetic pathway to methoxymycolic acids and ketomycolic acids,[15,17,36] and have been detected in *Mycobacterium smegmatis*, *M. tuberculosis* and *M. bovis* BCG Pasteur and Glaxo.[15,37]

The protected hydroxy-mycolic acids, **53**, **55** and **61** were each oxidised to the corresponding ketones, **63**, **64** and **65**, respectively (Scheme 18).



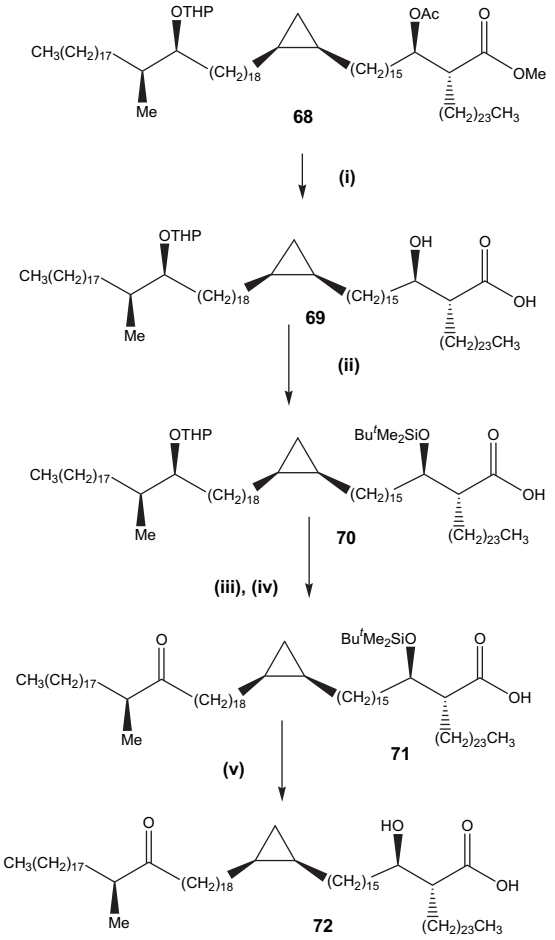
Scheme 18.

These protected ketomycolic acids each showed mass ions in MALDI MS that corresponded to the isotope pattern for one of the components in a keto-mycolate fraction separated from mycolic acids isolated from *Mycobacterium avium*.[38,39] These were then deprotected with lithium hydroxide in THF–methanol–water for 18 h at 45 °C to give the corresponding free mycolic acid in each case. The product from **63** showed an $[\alpha]_D^{26}$ +4.9 (*c* 1.02, $CHCl_3$). In the same way, hydrolysis of **65** gave a product with identical spectroscopic properties and an $[\alpha]_D^{26}$ +4.4 (*c* 0.70, $CHCl_3$). On this basis, the hydrolysis conditions had caused the epimerization of the methyl group adjacent to the carbonyl to give the same acid **66** in each case (Scheme 19).



Scheme 19.

In the same way, **64** gave **67**, $[\alpha]_D^{23}$+3.5 (*c* 0.59, $CHCl_3$). Given the small contribution of the *cis*-cyclopropane to the molecular rotations for these compounds, the closeness of the specific rotations for **66** and **67** is not unexpected. The hydrolysis was studied under a number of chemical conditions but all led to essentially complete epimerisation in the free ketomycolic acid. The literature reports that removal of mycolic acids from cell material by hydrolysis with base also leads to epimerisation.[6,7,10,15] However, there are reports that by using an enzyme system, the free keto-acid may be obtained without epimerisation.[15] When enzyme induced hydrolysis was tested for the synthetic mycolic acids **63** or **64**, no formation of the free mycolic acid could be observed and starting material was recovered. Instead, an alternative chemical approach was adopted. The TBDMS group of **53** (R=$SiMe_2Bu^t$) was selectively removed and the resulting alcohol was re-protected as a mixture of diasteromeric tetrahydropyranyl ethers **68** (Scheme 20).



Scheme 20. (i) LiOH, THF, MeOH, H_2O, 45 °C. 16 h (60%); (ii) imidazole, DMF, toluene, TBDMSCl, DMAP, 70 °C, 18 h; K_2CO_3, MeOH, THF, H_2O, then $KHSO_4$ to pH 2 (76%); (iii) pyridinium-*p*-toluenesulfonate, THF, MeOH, H_2O, 47 °C, 7 h (60%); (iv) PCC, CH_2Cl_2, rt, 2 h (74%); (v) pyridine, THF, HF-pyridine, 13 h, 42 °C (83%).

Deprotection of the two esters using lithium hydroxide in THF–methanol–water led to **69**. This was protected as the silyl ether **70** by reaction with an excess of TBDMS–Cl in dmf–imidazole–toluene, followed by reaction with potassium carbonate and methanol. This reaction first produced a bis-silyl protected molecule; the silyl protection on the acid was hydrolysed in the second stage of this process. Removal of the THP-group and oxidation then gave the ketone **71**; removal of the silyl group with HF.pyridine complex gave the keto-acid **72**. The specific rotation of **72** was +7.34 (*c*=0.79, $CHCl_3$), $[M]_D$ +92, in comparison to the epimeric mixture **66** above ($[\alpha]_D^{26}$ +4.4 (*c* 1.02, $CHCl_3$)), indicating that under these conditions the epimerization of the carbon adjacent to the ketone had not happened. This figure is in broad agreement with that for a ketomycolate mixture of homologues from BCG (containing around 1:10 *trans*-α-methyl-alkene to *cis*-alkene) which shows an $[M]_D$ when not epimerised of +77 and when epimerised of +42.[15] It is also in general agreement with the sum of the contributions of an *S*-α-methylketone unit ($[M]_D$ +44) and an *R*,*R*-hydroxy acid unit ($[M]_D$ +40),[15] assuming a very small contribution from the *cis*-cyclopropane. All of the peaks identified in the ^{13}C NMR spectrum of **72** were also present in a mixture of natural keto-mycolic acids from *M. avium* containing both *cis*- and α-methyl-*trans*-cyclopropanes.[38] The mass spectrum gave a molecular ion corresponding to the mass of the major component of the *cis*-cyclopropane containing keto-acid series in that natural fraction.[38,39]

The work described above provides routes to *cis*-cyclopropane containing keto- and hydroxy-mycolic acids with any absolute stereoisomers at the α-methyl group or the cyclopropane. Experiments to delineate the differing biological effects of such stereoisomers will be described elsewhere.

3. Experimental section

3.1. General

Chemicals used were obtained from commercial suppliers or prepared from them by methods described. Solvents which had to be dry, e.g. ether, tetrahydrofuran were dried over sodium wire. Petrol was of boiling point 40–60 °C. Reactions carried under inert conditions, were carried out under a slow stream of nitrogen. Those carried out at low temperatures were cooled using a bath of methylated spirit with liquid nitrogen. Silica gel (Merck 7736) and silica plates used for column and thin layer chromatography were obtained from Aldrich. Organic solutions were dried over anhydrous magnesium sulfate. GLC was carried out on a Perkin–Elmer Model 8410 on a capillary column (15 m×0.53 mm). IR spectra were carried out on a Perkin–Elmer 1600 F.T.IR spectrometer as liquid films. NMR spectra were recorded on an Advance 500 spectrometer . $[\alpha]_D$ values were recorded in $CHCl_3$ on a POLAAR 2001 Optical Activity polarimeter. Mass spectra were recorded on a Bruker Microtof or MALDI TOF spectrometers. IMS is industrial methylated spirit.

3.1.1. tert-Butyldimethyl-{(1R,2R)-2-methyl-1-[7-(tetrahydropyran-2-yloxy)heptyl]eicosyloxy}silane. Imidazole (1 g, 14.7 mmol) was added to a stirred solution of (8*R*,9*R*)-alcohol **8**[30] (3 g, 5.9 mmol) in dry DMF (35 ml) at rt followed by the addition of *tert*-butyldimethylsilylchloride (1.15 g, 7.65 mmol). After 18 h the reaction was warmed to 50 °C for 5 h, then quenched with water (200 ml) and extracted with dichloromethane (3×75 ml). The combined organic layers were washed with water (100 ml), dried and the solvent evaporated. Chromatography eluting with petrol/ether (5:1) gave a colourless oil, *tert*-butyldimethyl{(1*R*,2*R*)-2-methyl-1-[7-(tetrahydropyran-2-yloxy)heptyl]eicosyloxy}-silane (3.1 g, 84%), $[\alpha]_D^{24}$ +6.2 (*c* 1.42, $CHCl_3$) {Found $(M+Na)^+$: 647.5761, $C_{39}H_{80}NaO_3Si$ requires: 647.5769}. This showed δ_H: 4.58 (1H, br.t, *J* 2.9 Hz), 3.90–3.85 (1H, m), 3.74 (1H, dt, *J* 7.0, 9.8 Hz), 3.51–3.49 (2H, m), 3.38 (1H, dt, *J* 6.6, 9.5 Hz), 1.87–1.81 (1H, m), 1.75–1.70 (1H, m), 1.62–1.26 (50H, m, v. br.), 1.09–1.01 (1H, m), 0.89 (9H, s), 0.88 (3H, t, *J* 7.0 Hz), 0.80 (3H, d, *J* 6.6 Hz), 0.03 (3H, s), 0.02 (3H, s); δ_C: 98.9, 75.9, 67.7, 62.3, 37 8, 33.5, 32.5, 31.9, 30.8, 30.0, 29.9, 29.8, 29.77, 29.71(v. br.), 29.7, 29.5, 29.4, 27.7, 26.2, 26.0, 22.7, 19.7, 18.2, 14.4, 14.1, −4.2, −4.4; ν_{max}: 2825, 2853, 1464, 1253, 1079, 1035, 836, 773 cm^{-1}.

3.1.2. tert-Butyldimethyl-{(1S,2S)-2-methyl-1-[7-(tetrahydropyran-2-yloxy)heptyl]eicosyloxy}silane. tert-Butyldimethyl{(1*S*,2*S*)-2-methyl-1-[7-(tetrahydropyran-2-yloxy)heptyl]eicosyloxy}silane (7.50 g, 88%), a colourless oil, $[\alpha]_D^{24}$ −7.5 (*c* 1.34, $CHCl_3$) {Found $(M+Na)^+$: 647.5744, $C_{39}H_{80}NaO_3Si$ requires: 647.5769}, which showed an identical NMR spectrum to that above, was prepared in the same way from (8*S*,9*S*)-9-methyl-1-(tetrahydropyran-2-yloxy)hepta-cosan-8-ol.[22]

3.1.3. (8R,9R)-8-(tert-Butyldimethylsilanyloxy)-9-methylheptacosan-1-ol. Pyridinium-*p*-toluenesulfonate (0.73 g, 0.5 mol eq.) in methanol (40 ml) was stirred with *tert*-butyldimethyl-{(1*R*,2*R*)-2-methyl-1-[7-(tetrahydropyran-2-yloxy)-heptyl]eicosyloxy}silane (3.63 g, 5.8 mmol) in THF (30 ml) at 40 °C for 2.5 h. Satd aq sodium bicarbonate (10 ml) and water (20 ml) were added and extracted with ether (3×25 ml). The combined organic layers were dried and evaporated. Chromatography eluting with petrol/ether (5:1, 3:1, then 1:1) gave a colourless oil, (8*R*,9*R*)-8-(*tert*-butyldimethylsilanyloxy)-9-methyl heptacosan-1-ol (2.7 g, 86%), $[\alpha]_D^{23}$ +12.9 (*c* 1.39, $CHCl_3$) {Found $(M+Na)^+$: 563.5213, $C_{34}H_{72}NaO_2Si$ requires: 563.5194}. This showed δ_H: 3.65 (2H, q, *J* 6.5 Hz), 3.50 (1H, dt, *J* 3.5, 6.0 Hz), 1.58 (2H, quintet, *J* 7.3 Hz), 1.49–1.14 (44H, m, v. br.), 1.08–1.01 (1H, m), 0.90–0.86 (12H, s and t, *J* 6.9 Hz), 0.80 (3H, d, *J* 6.6 Hz), 0.03 (3H, s), 0.02 (3H, s); δ_C: 75.9, 63.1, 37.8, 33.5, 32.8, 32.4, 31.9, 30.0, 29.9, 29.7(v. br.), 29.68, 29.5, 29.4, 27.7, 26.0, 25.9, 25.7, 22.7, 18.2, 14.5, 14.1, −4.2, −4.4; ν_{max}: 3321, 2925, 2854, 1464, 1379, 1253, 1058 cm^{-1}.

3.1.4. (8S,9S)-8-(tert-Butyldimethylsilanyloxy)-9-methylheptacosan-1-ol. (8S,9S)-8-(*tert*-Butyldimethylsilanyloxy)-9-methylheptacosan-1-ol (94%), a colourless oil, $[\alpha]_D^{23}$ −12.5 (*c* 1.39, $CHCl_3$) {Found $(M+Na)^+$: 563.5195, $C_{34}H_{72}NaO_2Si$ requires: 563.5194}, which showed an identical NMR spectrum to that above, was prepared in the same way from *tert*-butyldimethyl{(1*S*,2*S*)-2-methyl-1-[7-(tetrahydropyran-2-yloxy)heptyl]-eicosyloxy}silane.

3.1.5. (8R,9R)-8-(tert-Butyldimethylsilanyloxy)-9-methylheptacosanal ***10***. (8*R*,9*R*)-8-(*tert*-Butyldimethylsilanyl-oxy)-9-methylheptacosan-1-ol (3.8 g, 7.04 mmol) in dichloromethane (70 ml) was added in portions with stirring to PCC (3.8 g, 17.6 mmol) in dichloromethane (160 ml). After 2 h, it was diluted with ether (250 ml), filtered through silica and the solvent was evaporated. Chromatography eluting with petrol/ether (3:1) gave a colourless oil, (8*R*,9*R*)-8-(*tert*-butyldimethylsilanyl-oxy)-9-methylheptacosanal **10** (3.7 g, 97%), $[\alpha]_D^{24}$ +7.2 (*c* 1.10, $CHCl_3$) {Found M^+: 538.5131, $C_{34}H_{70}O_2Si$ requires: 538.5145}. This showed δ_H: 9.77 (1H, t, *J* 1.6 Hz), 3.51–3.48 (1H, m), 2.43 (2H, dt, *J* 1.6, 7.3 Hz), 1.64 (2H, quintet, *J* 7.3 Hz), 1.48–1.20 (42H, m, v. br), 1.09–1.01 (1H, m), 0.90–0.88 (12H, s and t, *J* 6.9 Hz), 0.80 (3H, d, *J* 6.6 Hz), 0.03 (3H, s), 0.02 (3H, s); δ_C: 202.9, 75.9, 37.8, 33.4, 32.4, 31.9, 30.0, 29.72(v. br.), 29.68, 29.39, 29.21, 27.7, 25.9, 25.8, 22.7, 21.1, 18.2, 14.5, 14.2, −4.2, −4.4; ν_{max}: 2925, 2854, 1731, 1464, 1379, 1253, 1073 cm^{-1}.

3.1.6. (8S,9S)-8-(tert-Butyldimethylsilanyloxy)-9-methyl-heptacosanal ***11***. Aldehyde **11** (5.35 g, 97%), $[\alpha]_D^{25}$ −8.5 (*c* 1.01, $CHCl_3$) {Found $(M+Na)^+$: 561.5020, $C_{34}H_{70}NaO_2Si$ requires: 561.5037}, a colourless oil which showed an identical NMR spectrum to that above, was prepared in the same way from (8*S*,9*S*)-8-(*tert*-butyldimethyl-silanyloxy)-9-methylheptacosan-1-ol.

3.1.7. 2,2-Dimethylpropionic acid 10-(1-phenyl-1H-tetrazol-5-sulfonyl)decyl ester ***12***.

(i) Trimethylacetyl chloride (7.3 g, 60.8 mmol, 1.2 mol equiv) in dichloromethane (25 ml) was added over 15 min with stirring to 10-bromodecan-1-ol (12 g, 50.6 mmol), dichloromethane (80 ml), pyridine (8.2 ml, 101 mmol, 2 mol equiv) and 4-dimethylamino-pyridine (0.25 g, 2 mmol) at rt after 18 h, dil hydrochloric acid (150 ml) was added. The organic phase was washed with dil hydrochloric acid (100 ml) and brine (2×200 ml), dried and the solvent was evaporated. The residue was dissolved in petrol (200 ml) and filtered through silica washed with petrol (50 ml). The silica was washed with petrol/ether (1:1, 150 ml) and the solvent was evaporated to give a colourless oil, 2,2-dimethylpropionic acid 10-bromo-decyl ester (13.8 g, 85%) {Found: C, 56.2; H, 9.2; $C_{15}H_{29}BrO_2$ requires: C, 56.07; H, 9.10}. This showed δ_H: 4.05 (2H, t, *J* 6.6 Hz), 3.41 (2H, t, *J* 7.0 Hz), 1.86 (2H, quintet, *J* 7.2 Hz), 1.62 (2H, quintet, *J* 6.9 Hz), 1.44–1.40 (2H, m), 1.36–1.30 (10H, m), 1.20 (9H, s); δ_C: 178.6, 64.4, 38.7, 34.0, 32.8, 29.4, 29.3, 29.1, 28.7, 28.6, 28.1, 27.2, 25.9; ν_{max}: 2930, 2856, 1729, 1480, 1398, 1285, 1158 cm^{-1}.

(ii) 1-Phenyl-1*H*-tetrazol-5-thiol (5.75 g, 32.3 mmol), 2,2-dimethylpropionic acid 10-bromodecyl ester (10 g, 31.2 mmol), anhydrous potassium carbonate (9.5 g, 65.4 mmol) and acetone (160 ml) were vigorously stirred at rt for 18 h. Water (1 L) was added and the mixture was extracted with dichloromethane (1×150 ml, 2×25 ml). The combined organic phases were washed with brine (2×200 ml), dried and evaporated. Chromatography eluting with petrol/ether (7:2.5, then 1:1) gave a colourless oil, 2,2-dimethyl-propionic acid 10-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)decyl ester (12.1 g, 93%) {Found $(M+Na)^+$: 441.2292, $C_{22}H_{34}N_4NaO_2S$ requires: 441.2295}. This showed δ_H: 7.61–7.54 (5H, m), 4.04 (2H, t, *J* 6.6 Hz), 3.40 (2H, t, *J* 7.4 Hz), 1.82 (2H, quintet, *J* 7.4 Hz), 1.62 (2H, quintet, *J* 6.9 Hz), 1.48–1.42 (2H, m), 1.33–1.28 (10H, m), 1.20 (9H, s); δ_C: 178.6, 154.5, 133.8, 130.0, 129.7, 123.8, 64.4, 38.7, 33.3, 29.4, 29.3, 29.2, 29.1, 29.0, 28.6, 28.5, 27.2, 25.9; ν_{max}: 2929, 2856, 1726, 1500, 1461, 1388, 1285, 1159 cm^{-1}.

(iii) Ammonium molybdate (VI) tetrahydrate (13.9 g, 11.25 mmol) in 35% H_2O_2 (37 ml), prepared and cooled in an ice bath, was added with stirring to 2,2-dimethylpropionic acid 10-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)decyl ester (10 g, 23.9 mmol) in THF (140 ml) and IMS (280 ml) at 10 °C. After 2 h at rt, further ammonium molybdate (VI) tetrahydrate (7.5 g, 6.1 mmol) in 35% H_2O_2 (20 ml) was added. After 18 h, the mixture was poured into water (1.2 L) and extracted with dichloromethane (1×200 ml, 3×30 ml). The combined organic phases were washed with water (500 ml), dried and evaporated. Chromatography eluting with petrol/ether (3:1, then 1:1) gave a yellow oil, 2,2-dimethylpropionic acid 10-(1-phenyl-1*H*-tetrazole-5-sulfonyl)decyl ester **12** (10.5 g, 97%) {Found $(M+Na)^+$: 473.2186, $C_{22}H_{34}N_4NaO_4S$ requires: 473.2199}. This showed δ_H: 7.1–7.69 (2H, m), 7.63–7.60 (3H, m), 4.04 (2H, t, *J* 6.6 Hz), 3.75–3.72 (2H, m), 2.01–1.94 (2H, m), 1.62 (2H, quintet, *J* 6.9 Hz), 1.50 (2H, quintet, *J* 7.4 Hz), 1.34–1.29 (10H, m), 1.20 (9H, s); δ_C: 178.6, 153.4, 133.0, 131.4, 129.7, 125.0, 64.3, 55.9, 38.7, 29.3, 29.1, 29.0, 28.8, 28.5, 28.1, 27.2, 25.8, 21.9; ν_{max}: 2930, 2857, 1725, 1498, 1480, 1342, 1286, 1154 cm^{-1}.

*3.1.8. 2,2-Dimethylpropionic acid (18R,19R)-18-(tert-butyldimethylsilanyloxy)-19-methylheptatriacontyl ester **13**.* Sulfone **12** (3.9 g, 8.7 mmol) was dissolved in dry THF (60 ml) and a solution of aldehyde **10** (3.8 g, 7.1 mmol) in dry THF (60 ml) was added at rt This was cooled to −10 °C and lithium bis(trimethylsilyl)amide (13 ml, 13.49 mmol, 1.9 mol equiv, 1.06 M) was added at −10 to −4 °C, then allowed to reach rt and stirred for 1.5 h. Ether (75 ml) and satd aq ammonium chloride (25 ml) were added. The organic phase was separated and the water layer was extracted with ether (2×75 ml). The combined organic layers were dried and the solvent was evaporated. Chromatography eluting with petrol/ether (10:0.6) gave a colourless oil, 2,2-dimethylpropionic acid (*E*/*Z*)-(18*R*,19*R*)-18-(*tert*-butyldimethylsilanyloxy)-19-methylheptatriacont-10-enyl ester (4.9 g, 92%) as a 2.3:1 mixture of isomers {Found $(M+Na)^+$: 785.7205, $C_{49}H_{98}NaO_3Si$ requires: 785.7177}. Palladium 10% on carbon (1.5 g) was added to a stirred solution of the above alkenes (4.94 g, 6.5 mmol) in ethanol (150 ml) and ethyl acetate (70 ml). Hydrogenation was carried out for 1 h. The solution was filtered through Celite and evaporated to give a pure colourless oil, 2,2-dimethylpropionic acid (18*R*,19*R*)-18-(*tert*-butyldimethylsilanyloxy)-19-methylheptatriacontyl ester **13** (4.9 g, 99%), $[\alpha]_D^{25}$ +4.8 (*c* 1.10, $CHCl_3$) {Found $(M+Na)^+$: 787.7355, $C_{49}H_{100}NaO_3Si$ requires: 787.7334}. This showed δ_H: 4.05 (2H, t, *J* 6.6 Hz), 3.51–3.48 (1H, m), 1.62 (2H, quintet, *J* 6.6 Hz), 1.49–1.26 (64H, m, v. br.), 1.20 (9H, s), 1.08–1.01 (1H, m), 0.90–0.87 (12H, m), 0.80 (3H, d, *J* 6.6 Hz), 0.03 (3H, s), 0.02 (3H, s); δ_C: 178.7, 75.9, 64.5, 38.7, 37.7, 33.5, 32.5(+), 31.9, 30.0, 29.9, 29.72 (v. br.), 29.68, 29.59, 29.55, 29.4, 29.3, 28.6, 27.7, 27.2, 26.0, 25.9, 22.7, 18.2, 14.4, 14.2, −4.2, −.4; ν_{max}: 2923, 2854, 1733, 1464, 1155, 836 cm^{-1}.

*3.1.9. 2,2-Dimethylpropionic acid (18S,19S)-18-(tert-butyldimethylsilanyloxy)-19-methylheptatriacontyl ester **14**.* 2,2-Dimethylpropionic acid (18*S*,19*S*)-18-(*tert*-butyldimethylsilanyloxy)-19-methylheptatriacontyl ester **14** (97%) {Found $(M+Na)^+$: 787.7327, $C_{49}H_{100}NaO_3Si$ requires: 787.7334}, was obtained as a colourless oil in the same way from **12** and (8*S*,9*S*)-aldehyde **11**. It showed an identical NMR spectrum to that above, $[\alpha]_D^{25}$ −4.8 (*c* 0.88, $CHCl_3$).

*3.1.10. (18R,19R)-18-(tert-Butyldimethylsilanyloxy)-19-methyl-heptatriacontan-1-ol **15**.* Ester **13** was added over 15 min to a suspension of lithium aluminium hydride (0.37 g, 9.6 mmol) in THF (60 ml) at −20 °C under nitrogen. After refluxing the mixture for 1 h, satd aq sodium sulfate was added at −20 °C until a precipitate had formed. THF (60 ml) was added and the mixture was stirred at rt for 30 min, filtered through silica and the solvent evaporated. Chromatography eluting with petrol/ether (3:1, then 4:3) gave a colourless oil, (18*R*,19*R*)-18-(*tert*-butyldimethylsilanyloxy)-19-methylheptatriacontan-1-ol **15** (4.3 g, 98%), $[\alpha]_D^{24}$ +5.1 (*c* 0.95, $CHCl_3$) {Found $(M+H)^+$: 681.6921, $C_{44}H_{93}O_2Si$ requires: 681.6939}. This showed δ_H: 3.65 (2H, q, *J* 6.7 Hz), 3.52–3.48 (1H, m), 1.58 (2H, quintet, *J* 6.9 Hz), 1.48–1.12 (65H, m, v. br.), 1.08–1.01 (1H, m), 0.90–0.88 (12H, m, including a singlet resonating at δ 0.89 for the *tert*-butyl group), 0.80 (3H, d *J* 6.7 Hz), 0.03 (3H, s), 0.02 (3H, s); δ_C: 75.9, 63.1, 37.7, 33.5, 32.8, 32.4, 31.9, 30.0, 29.9, 29.7, 29.6(v. br.), 29.5, 29.4, 27.7, 26.0, 25.9, 25.8, 22.7, 18.2, 14.4, 14.2, −.2, −4.4; ν_{max}: 3330, 2927, 2848, 1465, 1378, 1253, 1058 cm^{-1}.

*3.1.11. (18S,19S)-18-(tert-Butyldimethylsilanyloxy)-19-methylheptatriacontan-1-ol **16**.* (18*S*,19*S*)-18-(*tert*-Butyldimethylsilanyloxy)-19-methylheptatriacontan-1-ol **16** (95%), was obtained in the same way from 2,2-dimethylpropionic acid (18*S*,19*S*)-18-(*tert*-butyldimethylsilanyloxy)-19-methylheptatriacontyl ester as a colourless oil, $[\alpha]_D^{24}$ −5.1 (*c* 1.02, $CHCl_3$) {Found $(M+H)^+$: 681.6948, $C_{44}H_{93}O_2Si$ requires: 681.6939}. This showed an identical NMR spectrum to that above.

*3.1.12. (18R,19R)-18-(tert-Butyldimethylsilanyloxy)-19-methylheptatriacontanal **17**.* Alcohol **15** (2.0 g, 2.94 mmol) in dichloromethane (30 ml) was added in portions to a stirred solution of PCC (1.6 g, 7.35 mmol, 2.5 mol equiv) in dichloromethane (120 ml) at rt After 2 h, it was diluted with ether (150 ml), filtered through silica and the solvent evaporated. Chromatography eluting with petrol/ether (4:1) gave a colourless oil, (18*R*, 19*R*)-18-(*tert*-butyldimethylsilanyloxy)-19-methylheptatriacontanal **17** (1.95 g, 98%), $[\alpha]_D^{23}$ +5.8 (*c* 0.92, $CHCl_3$) {Found M^+: 678.6723, $C_{44}H_{90}O_2Si$ requires: 678.6710}. This showed δ_H: 9.77 (1H, t, *J* 1.6 Hz), 3.51–3.48 (1H, m), 2.42 (2H, dt, *J* 1.6, 7.3 Hz), 1.64 (2H, quintet, *J* 7.3 Hz), 1.50–1.13 (62H, m, v. br.), 1.08–1.01 (1H, m), 0.90–0.88 (12H, m, including a s), 0.80 (3H, d, *J* 6.7 Hz), 0.03 (3H, s), 0.02 (3H, s); δ_C: 202.9, 75.9, 43.9, 37.7, 33.5, 32.5, 31.9, 30.0, 29.9 (v. br.), 29.65, 29.6, 29.5, 29.4, 29.2, 27.7, 26.0, 25.9, 22.7, 22.1, 18.2, 14.4, 14.1, −4.2, −4.4; ν_{max}: 2925, 2854, 1731, 1465, 1379, 1253, 1072 cm^{-1}.

*3.1.13. (18S,19S)-18-(tert-Butyldimethylsilanyloxy)-19-methylheptatriacontanal **18**.* Aldehyde **18** (5.00 g, 95%) $[\alpha]_D^{23}$ −5.15 (*c* 0.95, $CHCl_3$) {Found $(M+Na)^+$: 701.6590, $C_{44}H_{90}NaO_2Si$ requires: 701.6602} was prepared in the same way from alcohol **16** as a colourless oil. This showed an identical NMR spectrum to that above.

*3.1.14. Butyric acid (1R,2S)-2-[(19R,20R)-19-(tert-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropylmethyl ester **20**.* Aldehyde **17** (1.87 g, 2.76 mmol) in dry THF (20 ml) was added with stirring to

butyric acid (1*R*,2*S*)-2-(1-phenyl-1*H*-tetrazole-5-sulfonylmethyl)-cyclopropyl-methyl ester **19**[21–23] (1.2 g, 3.31 mmol) in dry THF (20 ml) at rt, cooled to −10 °C and lithium bis-(tri-methylsilyl) amide (4.9 ml, 5.2 mmol, 1.06 M) was added at −12 to −5 °C. After 1.5 h at rt, dichloromethane (60 ml) and satd aq ammonium chloride (50 ml) were added and extracted. The aqueous layer was re-extracted with dichloromethane (2×30 ml), the combined organic layers were washed with water (100 ml), dried and evaporated. Chromatography eluting with petrol/ether (10:0.5) gave a colourless oil, butyric acid (1*R*,2*S*)-2-[(*E*/*Z*)-(19*R*, 20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacont-1-enyl]cyclopropylmethyl ester (2.05 g, 91%) as a 1.6:1 mixture of two isomers {Found $(M+Na)^+$: 839.7642, $C_{53}H_{104}NaO_3Si$ requires: 839.7647}. The above alkenes (2.5 g, 3.06 mmol) and 2,4,6-tri-isopropylbenzenesulphonyl hydrazide (3.2 g, 10.7 mmol) were dissolved in dry THF (50 ml) and stirred at 40 °C for 3 h. Further TPBSH (1 g, 3.34 mmol) was added and stirred at 40 °C for 24 h. The mixture was diluted with petrol/ether (1:1, 200 ml) and aq sodium hydroxide (80 ml, 2%) was added and extracted. The aqueous layer was re-extracted with petrol/ether (1:1, 2×60 ml) and the combined organic layers were washed with water (80 ml), dried and evaporated. Chromatography eluting with petrol/ether (25:1) gave a colourless oil containing a small amount of alkene. The mixture was dissolved in dichloro-methane (35 ml) and water (35 ml) then acetic acid (1 ml), cetrimide (0.15 g) and potassium permanganate (0.7 g) were added and stirred at rt for 1 h. Sodium metabisulfite was added until the dark colour disappeared and the mixture was extracted with dichloromethane (3×30 ml). The combined organic layers were dried, filtered and evaporated. Chromatography eluting with petrol/ether (25:1) gave a colourless oil, butyric acid (1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropylmethyl ester **20** (1.75 g, 70%), $[\alpha]_D^{24}$ +9.8 (*c* 1.26, $CHCl_3$) {Found $(M+Na)^+$: 841.7820, $C_{53}H_{106}NaO_3Si$ requires: 841.7803}. This showed δ_H: 4.20 (1H, dd, *J* 6.9, 11.7 Hz), 3.95 (1H, dd, *J* 8.5, 11.7 Hz), 3.51 (1H, dt, *J* 3.5, 6.3 Hz), 2.31 (2H, t, *J* 7.4 Hz), 1.68 (2H, sext, *J* 7.4 Hz), 1.50–1.13 (71H, m, v. br.), 1.16–1.12 (1H, m), 1.08–1.01 (1H, m), 0.97 (3H, t, *J* 7.4 Hz), 0.91–0.88 (12H, s and t, *J* 6.9 Hz), 0.81 (3H, d, *J* 6.9 Hz), 0.75 (1H, dt, *J* 5.1, 8.5 Hz), 0.04 (3H, s), 0.03 (3H, s), 0.01 (1H, br. q, *J* 5.1 Hz); δ_C: 173.8, 75.9, 65.1, 37.8, 36.4, 33.6, 32.5, 31.9, 30.0, 29.9, 29.7(v. br.), 29.6, 29.4, 28.6, 27.7, 26.0, 25.9, 22.7, 18.8, 18.2, 16.3, 14.4, 14.2, 14.1, 13.7, 9.8, −4.2, −4.4; ν_{max}: 2924, 2854, 1739, 1665, 1252, 1181 cm^{-1}.

*3.1.15. {(1R,2S)-2-[(19R,20R)-19-(tert-Butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}-methanol **21**.* Ester **20** (1.48 g, 1.81 mmol) in THF (10 ml) was added over 15 min to a suspension of lithium aluminium hydride (0.17 g, 4.35 mmol) in THF (25 ml) at 0 °C under nitrogen. The mixture was refluxed for 1 h, then cooled to 0 °C and satd aq sodium sulfate was added until a white precipitate had formed. THF (50 ml) was added and the mixture was stirred at rt for 30 min, filtered through silica and the solvent was evaporated. Chromatography eluting with petrol/ether (4:3) gave a colourless oil, {(1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}methanol **21** (1.31 g, 97%), $[\alpha]_D^{22}$ +10.5 (*c* 0.89, $CHCl_3$) {Found $(M+Na)^+$: 771.7363, $C_{49}H_{100}NaO_2Si$ requires: 771.7385}. This showed δ_H: 3.66 (1H, dd, *J* 7, 11 Hz), 3.59 (1H, dd, *J* 8, 11 Hz), 3.52–3.48 (1H, m), 1.51–1.21 (71H, m, v. br.), 1.15–1.0 (2H, m), 0.90–0.88 (12H, s and t, *J* 6.7 Hz), 0.80 (3H, d, *J* 6.6 Hz), 0.71 (1H, dt, *J* 4.4, 8.2 Hz), 0.04 (3H, s), 0.03 (3H, s), −.03 (1H, br. q, *J* 5.4 Hz); δ_C: 75.9, 63.4, 37.7, 33.5, 32.5, 31.9, 30.2, 30.0, 29.9, 29.7(v. br.), 29.67, 29.65, 29.6, 29.4, 28.6, 27.7, 26.0, 25.9, 22.7, 18.2, 16.2, 14.4, 14.1, 9.5, −4.2, −4.4; ν_{max}: 3346, 2924, 2853, 1465, 1253, 1033 cm^{-1}.

*3.1.16. (1R,2S)-2-[(19R,20R)-19-(tert-Butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropane-carbaldehyde **22**.* A solution of alcohol **21** (0.9 g, 1.2 mmol) in dichloromethane (25 ml) was added in portions to PCC (0.65 g, 3.0 mmol) stirred in dichloromethane (100 ml) at rt After 2 h, it was diluted with ether (150 ml), filtered through silica and the solvent was evaporated. Chromatography eluting with petrol/ether (6:1) gave a colourless oil, (1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropanecarbaldehyde **22** (0.9 g, 100%), $[\alpha]_D^{25}$ +7.6 (*c* 1.19, $CHCl_3$) {Found $(M+H)^+$: 747.7397, $C_{49}H_{99}O_2Si$ requires: 747.7409}. This showed δ_H: 9.36 (1H, d, *J* 5.7 Hz), 3.52–3.49 (1H, m), 1.87 (1H, ddt, *J* 8.2, 5.7, 5.4 Hz), 1.62–1.56 (2H, m), 1.50–1.18 (71H, m, v. br.), 1.07–1.01 (1H, m), 0.90–0.87 (12H, including a singlet at δ 0.89), 0.80 (3H, d, *J* 6.7 Hz), 0.04 (3H, s), 0.03 (3H, s); δ_C: 201.7, 75.9, 37.7, 33.6, 32.5, 31.9, 30.0, 29.99, 29.9, 29.7(v. br.), 29.7, 29.67, 29.6, 29.5, 29.4, 29.3, 28.2, 27.8, 27.7, 26.0, 25.9, 24.8, 22.7, 18.2, 14.7, 14.4, 14.1, −4.2, −4.4; ν_{max}: 2925, 2853, 1706, 1465, 1253 cm^{-1}.

*3.1.17. Butyric acid (1R,2S)-2-[(19S,20S)-19-(tert-butyldimethylsilanyloxy)-20-methyloctatriacontyl]-cyclopropylmethyl ester **23**.* A solution of (18*S*, 19*S*)-aldehyde **18** (1.8 g, 2.65 mmol) in dry THF (10 ml) was added with stirring to sulfone **19** (1.26 g, 3.45 mmol) in dry THF (20 ml) at rt, cooled to −5 °C and lithium bis-(trimethyl-silyl)amide (4.87 ml, 5.17 mmol, 1.06 M) was added at −5 °C under nitrogen. The solution was stirred for 1.5 h at rt. Work up as above gave a colourless oil, butyric acid (1*R*,2*S*)-2-[(*E*/*Z*)-(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacont-1-enyl]cyclopropylmethyl ester (1.8 g, 83%) as a 2.5:1 mixture of isomers. The mixture (1.7 g, 7.28 mmol) and 2,4,6-tri-isopropylbenzenesulphonyl hydrazide (2.17 g, 7.28 mmol) were stirred in dry THF (50 ml) at 40 °C for 3 h. Further TPBSH (1.5 g, 5.026 mmol) was added and stirred at 40 °C for 24 h. The mixture was worked up and purified as above to give butyric acid (1*R*,2*S*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropylmethyl ester **23** (1.35 g, 76%), $[\alpha]_D^{24}$ −0.78 (*c* 1.54, $CHCl_3$) {Found $(M+Na)^+$: 841.7823, $C_{53}H_{106}NaO_3Si$ requires: 841.7803} as a colourless oil. This showed an essentially identical NMR spectrum to that of its diastereomer **20** above.

*3.1.18. {(1R,2S)-2-[(19S,20S)-19-(tert-Butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}methanol **24**.* Ester **23** (1.3 g, 1.58 mmol) in dry THF (5 ml) was added dropwise over 15 min to a suspension of lithium aluminium hydride (0.09 g, 2.38 mmol) in THF (5 ml) at 0 °C under nitrogen. The mixture was refluxed for 1 h. Work up as above gave a colourless oil, {(1*R*,2*S*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}methanol (1.12 g, 95%), $[\alpha]_D^{22}$+1.7 (*c* 1.02, $CHCl_3$) {Found $(M+Na)^+$: 771.7409, $C_{49}H_{100}NaO_2Si$ requires: 771.7385}, which showed an essentially identical NMR spectrum to that of its diastereomer **21**.

*3.1.19. (1R,2S)-2-[(19S,20S)-19-(tert-Butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropanecarbaldehyde **25**.* A solution of {(1*R*,2*S*)-alcohol **24** (0.76 g, 1.02 mmol) in dichloromethane (20 ml) was added in portions with stirring to PCC (0.66 g, 3.05 mmol) in dichloromethane (30 ml) at rt. After 2 h, work up as above gave (1*R*,2*S*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropanecarbaldehyde **25** (0.73 g, 96%), as a colourless oil, $[\alpha]_D^{25}$ −4.89 (*c* 0.92, $CHCl_3$) {Found $(M+Na)^+$: 769.7195, $C_{49}H_{98}NaO_2Si$ requires: 769.7228}, which showed an essentially identical NMR spectrum to that of its diastereomer **22**.

*3.1.20. Butyric acid (1S,2R)-2-[(19S,20S)-19-(tert-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropylmethyl ester **27**.* A solution of (18*S*,19*S*)-aldehyde **18** (2.1 g, 3.09 mmol) in dry THF (10 ml) was added with stirring to sulfone **26** (1.46 g, 4.02 mmol) in dry THF (20 ml) at rt, cooled to −5 °C and lithium bis-(trimethylsilyl) amide (5.69 ml, 6.03 mmol, 1.06 M) was added. The solution was stirred for 1.5 h at rt when work up as above gave butyric acid (1*S*,2*R*)-2-[(*E*/*Z*)-(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacont-

1-enyl]cyclopropylmethyl ester (2.2 g, 87%) as a 1.6:1 mixture of isomers. The mixture (2.0 g, 2.44 mmol) and 2,4,6-tri-isopropylbenzenesulphonyl hydrazide (2.55 g, 8.57 mmol) were stirred in dry THF (50 ml) at 40 °C for 3 h. Further TPBSH (1.5 g, 5.02 mmol) was added and stirred at 40 °C for 24 h. Work up and purification as above gave butyric acid (1*S*,2*R*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropylmethyl ester **27** (1.6 g, 80%), $[\alpha]_D^{24}$ −8.8 (*c* 1.30, $CHCl_3$) {Found $(M+Na)^+$: 841.7786, $C_{53}H_{106}NaO_3Si$ requires: 841.7803} as a colourless oil which showed an identical NMR spectrum to that of **20** above.

*3.1.21. {(1S,2R)-2-[(19S,20S)-19-(tert-Butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}methanol **28**.* (1*S*,2*R*)-Ester **29** (1.4 g, 1.71 mmol) in dry THF (5 ml) was added over 15 min to a suspension of lithium aluminium hydride (0.1 g, 2.63 mmol) in THF (5 ml) at 0 °C under nitrogen, then refluxed for 1 h. Work up as above gave {(1*S*,2*R*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}methanol **28** (1.19 g, 93%), $[\alpha]_D^{22}$ −5.03 (*c* 2.68, $CHCl_3$) {Found $(M+Na)^+$: 771.7348, $C_{49}H_{100}NaO_2Si$ requires: 771.7385}, a colourless oil showing an identical NMR spectrum to that of **21**.

*3.1.22. (1S,2R)-2-[(19S,20S)-19-(tert-Butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropanecarbaldehyde **29**.* {(1*S*,2*R*)-Alcohol **28** (1.01 g, 1.43 mmol) in dichloromethane (10 ml) was added in portions to a stirred solution of PCC (0.92 g, 4.29 mmol) in dichloromethane (50 ml) at rt. After 2 h, work up as above gave (1*S*,2*R*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropanecarbaldehyde **29** (0.88 g, 82%), $[\alpha]_D^{18}$ −12.00 (*c* 0.40, $CHCl_3$) {Found $(M+Na)^+$: 769.7211, $C_{49}H_{98}NaO_2Si$ requires: 769.7228}, as a colourless oil which showed an identical NMR spectrum of **22** above.

*3.1.23. Acetic acid (S)-1-(2-benzyloxyethyl)-but-3-enyl ester **41**.* Acetic anhydride (80 ml) then anhydrous pyridine (80 ml) were added with stirring to (*S*)-1-benzyloxyhex-5-en-3-ol (see Supplementary data) (23.5 g, 114.1 mmol) in dry toluene (180 ml) at rt After 18 h, it was diluted with toluene (100 ml) and the solvent was evaporated. Chromatography eluting with petrol/ether (6:1) gave a colourless oil, acetic acid (*S*)-1-(2-benzyloxyethyl)-but-3-enyl ester **41** (28.05 g, 99%), $[\alpha]_D^{23}$ +49.0 (*c* 1.13, $CHCl_3$) {Found $(M+H)^+$: 249.1485, $C_{15}H_{21}O_3$ requires: 249.1485}. This showed δ_H: 7.37–7.27 (5H, m), 5.76 (1H, ddt, *J* 17.0, 10.4, 7.0 Hz), 5.13–5.06 (3H, m), 4.50 (1H, d, *J* 12.0 Hz), 4.47 (1H, d, *J* 12.0 Hz), 3.54–3.46 (2H, m), 2.40–2.30 (2H, m), 2.00 (3H, m), 1.94–1.82 (2H, m); δ_C: 170.6, 138.3, 133.5, 128.3, 127.7, 127.6, 117.8, 73.0, 70.8, 66.6, 38.8, 33.7, 21.1; ν_{max}: 3066, 3031, 2923, 2861, 1737, 1643, 1496, 1454, 1372, 1241, 1100, 1026 cm^{-1}.

*3.1.24. (R)-3-Acetoxy-5-benzyloxypentanoic acid **42**.* Ester **41** (17.8 g, 71.77 mmol) was stirred in dry DMF (450 ml) and oxone (176.5 g, 287.1 mmol) then OsO_4 2.5% in 2-methyl-2-propanol (9 ml, 0.72 mmol) were added at 10 °C. The temperature was allowed to reach 32 °C for 3 h. The mixture was treated with water (3 L) and extracted with ethyl acetate (1×500 ml, 2×250 ml). The combined organic layers were washed with water (700 ml), dried and evaporated. Chromatography eluting with petrol/ethyl acetate (1:1 then 1:2) gave a colourless oil, (*R*)-3-acetoxy-5-benzyloxypentanoic acid **42** (14.85 g, 78%), $[\alpha]_D^{22}$ +15.2 (*c* 0.89, $CHCl_3$) {Found $(M+H)^+$: 267.1216, $C_{14}H_{19}O_5$ requires: 267.1227}, δ_H: 7.37–7.27 (5H, m), 5.36 (1H, quintet, *J* 6.3 Hz), 4.49 (2H, br.t, *J* 12.5 Hz), 3.56 (1H, dt, *J* 15.8, 6.0 Hz), 3.53 (1H, dt, *J* 16.1, 6.3 Hz), 2.71 (1H, dd, *J* 5.7, 15.8 Hz), 2.69 (1H, dd, *J* 6.9, 16.1 Hz), 2.01 (3H, s), 1.97 (2H, br.q, *J* 6.0 Hz); δ_C: 175.4, 170.4, 138.0, 128.4, 127.73, 127.66, 73.1, 68.2, 66.2, 38.9, 33.8, 21.0; ν_{max}: 3457, 3064, 3032, 2930, 2864, 1740, 1680, 1454, 1374, 1242, 1176, 1100 cm^{-1}.

*3.1.25. (R)-5-Benzyloxy-3-hydroxypentanoic acid methyl ester **43**.* Conc. H_2SO_4 (70 drops) was added to a stirred solution of acid **42** (14.75 g, 55.45 mmol) in methanol (300 ml) and refluxed for 3.5 h. The methanol was evaporated and ethyl acetate (250 ml) and satd aq $NaHCO_3$ (200 ml) added. The aqueous layer was extracted with ethyl acetate (2×150 ml) and the combined organic layers were dried and evaporated. Chromatography eluting with petrol/ethyl acetate (3:2) gave a colourless oil, (*R*)-5-benzyloxy-3-hydroxypentanoic acid methyl ester **43** (10.23 g, 78%), $[\alpha]_D^{26}$ −12.2 (*c* 1.23, $CHCl_3$) {Found $(M+Na)^+$: 261.1085, $C_{13}H_{18}NaO_4$ requires: 261.1097}. This showed δ_H: 7.37–7.28 (5H, m), 4.53 (2H, s), 4.26 (1H, tdd, *J* 6.3, 4.1, 7.9 Hz), 3.72 (1H, ddd, *J* 5.1, 6.3, 9.5 Hz), 3.71 (3H, s), 3.66 (1H, ddd, *J* 5.1, 6.9, 9.5 Hz), 3.38 (1H, d, *J* 3.2 Hz), 2.52 (2H, d, *J* 6.3 Hz), 1.87–1.77 (2H, m); δ_C: 172.8, 138.0, 128.4, 127.7, 127.6, 73.3, 68.0, 67.0, 51.7, 41.4, 36.0; ν_{max}: 3467, 3031, 2951, 2864, 1737, 1496, 1438, 1168, 1100 cm^{-1}.

*3.1.26. (R)-2-((R)-3-Benzyloxy-1-hydroxypropyl)pent-4-enoic acid methyl ester **44**.* Diisopropylamine (7.86 g, 77.69 mmol) was dissolved in dry THF (100 ml) and cooled to −78 °C. MeLi (54.38 ml, 81.57 mmol, 1.5 M) was added and stirred to +16 °C for 30 min then re-cooled to −61 °C and (*R*)-5-benzyloxy-3-hydroxypentanoic acid methyl ester **43** (8.6 g, 36.13 mmol) in dry THF (50 ml) was added and stirred at −45 °C for 1 h, −20 °C for 40 min and then at −20 to −10 °C for 20 min. It was re-cooled to −62 °C and allyl iodide (5.0 ml, 54.21 mmol) in dry THF (20 ml) and HMPA (12.57 ml, 72.27 mmol) was added and stirred at −45 °C for 1 h., −45 to −20 °C for 30 min and then −20 °C for 30 min. Further allyl iodide (0.9 ml) was added and stirred at −20 to −10 °C for 30 min and then −10 °C for 30 min. Satd aq ammonium chloride (70 ml) was added and extracted with ether/ethyl acetate (1:1, 3×100 ml), dried and the solvent evaporated. Chromatography eluting with petrol/ethyl acetate (2:1) gave a colourless oil, (*R*)-2-((*R*)-3-benzyloxy-1-hydroxypropyl)pent-4-enoic acid methyl ester **44** (7.64 g, 76%), $[\alpha]_D^{21}$ −6.9 (*c* 1.09, $CHCl_3$) {Found $(M+H)^+$: 279.1582, $C_{16}H_{23}O_4$ requires: 279.1591}. This showed δ_H: 7.38–7.28 (5H, m), 5.75 (1H, ddt, *J* 17.0, 10.1, 6.9 Hz), 5.12–5.03 (2H, m), 4.52 (2H, s), 3.97 (1H, dtd, *J* 8.8, 5.7, 2.9 Hz), 3.72 (1H, ddd, *J* 4.8, 6.0, 9.2 Hz), 3.70 (3H, s), 3.66 (1H, ddd, *J* 5.1, 7.4, 9.5 Hz), 3.20 (1H, d, *J* 5.7 Hz), 2.58 (1H, td, *J* 5.7, 8.8 Hz), 2.47–2.35 (2H, m), 1.88–1.74 (2H, m); δ_C: 174.8, 137.9, 134.9, 128.4, 127.7, 127.6, 117.1, 73.3, 70.9, 68.3, 51.6, 51.0, 34.6, 33.3; ν_{max}: 3494, 3066, 3030, 2951, 2863, 1735, 1643, 1438, 1367, 1170, 1100 cm^{-1}.

3.1.27. (R)-2-[(R)-3-Benzyloxy-1-(tert-butyldimethylsilanyloxy)-propyl]pent-4-enoic acid methyl ester. Imidazole (3.67 g, 53.96 mmol) was added to a stirred solution of ester **44** (6.0 g, 21.83 mmol) in dry DMF (100 ml) at rt, followed by addition of *tert*-butyldimethylchlorosilane (4.23 g, 28.06 mmol) and stirred at 45 °C for 18 h. The mixture was quenched with water (350 ml) and extracted with dichloromethane (3×200 ml). The combined organic layers were washed with water (200 ml), dried and the solvent was evaporated. Chromatography eluting with petrol/ether (4:1) gave a colourless oil, (*R*)-2-[(*R*)-3-benzyloxy-1-(*tert*-butyldimethylsilanyloxy)propyl]-pent-4-enoic acid methyl ester (7.4 g, 87%), $[\alpha]_D^{26}$ −17.2 (*c* 0.93, $CHCl_3$) {Found $(M+Na)^+$: 415.2256, $C_{22}H_{36}NaO_4Si$ requires: 415.2275}. This showed δ_H: 7.37–7.27 (5H, m), 5.73 (1H, ddt, *J* 17.0, 10.1, 6.9 Hz), 5.06–4.97 (2H, m), 4.49 (2H, br.t, *J* 12.3 Hz), 4.13 (1H, br.q, *J* 5.7 Hz), 3.65 (3H, s), 3.59 (1H, td, *J* 6.3, 9.2 Hz), 3.55 (1H, td, *J* 6.6, 9.5 Hz), 2.69–2.65 (1H, m), 2.37–2.33 (2H, m), 1.84–1.80 (2H, m), 0.87 (9H, s), 0.05 (6H, s); δ_C: 173.7, 138.5, 135.9, 128.3, 127.6, 127.5, 116.3, 72.9, 70.2, 66.3, 51.7, 51.3, 33.7, 31.3, 25.7, 17.9, −4.4, −4.9; ν_{max}: 3032, 2954, 2930, 2857, 1739, 1643, 1437, 1361, 1254, 1171, 1100 cm^{-1}.

*3.1.28. (2R,3R)-5-Benzyloxy-3-(tert-butyldimethylsilanyloxy)-2-(2-oxoethyl)pentanoic acid methyl ester **45**.* 2,6-Lutidine (2.36 g, 21.98 mmol), OsO_4 2.5% in 2-methyl-2-propanol (2 ml, 0.2 mmol), and then $NaIO_4$ (9.4 g, 43.96 mmol) were added with stirring to the above ester (4.0 g, 10.99 mmol) in 1,4-dioxane–water (160 ml, 3:1)

at rt. The reaction was stirred at 25 °C for 2 h, when water (300 ml) and dichloromethane (300 ml) were added. The water layer was extracted with dichloromethane (2×100 ml) and the combined organic layers were washed with brine (200 ml), dried and evaporated. Chromatography eluting with petrol/ether (2:1) gave a colourless oil, (2*R*,3*R*)-5-benzyloxy-3-(*tert*-butyldimethylsilanyloxy)-2-(2-oxoethyl)pentanoic acid methyl ester **45** (3.52 g, 88%), $[\alpha]_D^{26}$ −18.4 (*c* 0.97, $CHCl_3$) {Found $(M+H)^+$: 395.2244, $C_{21}H_{35}O_5Si$ requires: 395.2248}. This showed δ_H: 9.81 (1H, s), 7.37–7.28 (5H, m), 4.50 (1H, d, *J* 12.0 Hz), 4.45 (1H, d, *J* 12.0 Hz), 4.27 (1H, td, *J* 4.4, 7.9 Hz), 3.68 (3H, s), 3.54–3.50 (2H, m), 3.23 (1H, ddd, *J* 3.2, 7.6, 10.4 Hz), 2.97 (1H, ddd, *J* 1.0, 10.4, 18.3 Hz), 2.70 (1H, dd, *J* 3.2, 18.3 Hz), 1.71–1.63 (2H, m), 0.87 (9H, m), 0.08 (3H, s), 0.07 (3H, s); δ_C: 200.4, 172.4, 138.3, 128.3, 127.6, 127.5, 72.8, 68.8, 66.5, 52.0, 45.3, 40.0, 33.7, 25.7, 17.9, −4.7, −4.9; ν_{max}: 3031, 2954, 2930, 2857, 1736, 1496, 1437, 1315, 1254, 1100 cm^{-1}.

*3.1.29. (R)-2-[(R)-3-Benzyloxy-1-(tert-butyldimethylsilanyloxy)-propyl]hexacosanoic acid methyl ester **46**.* Lithium bis(trimethylsilyl)amide (23.16 ml, 24.54 mmol) was added with stirring to ester **45** (4.39 g, 11.14 mmol) and 5-(docosane-1-sulfonyl)-1-phenyl-1*H*-tetrazole **47** (see Supplementary data, 8.48 g, 16.36 mmol) in dry THF (150 ml) at −8 °C under argon. After 3 h at rt, it was quenched with satd aq ammonium chloride (120 ml), extracted with petrol/ether (3×150 ml, 10:1), dried and the solvent was evaporated. Chromatography eluting with petrol/ether (20:1) gave a colourless oil, (*E*/*Z*)-(*R*)-2-[(*R*)-3-benzyloxy-1-(*tert*-butyldimethylsilanyloxy)-propyl]tetracos-4-enoic acid methyl ester (*R*)-2-[(*R*)-3-benzyloxy-1-(*tert*-butyldimethylsilanyloxy)propyl]hexacos-4-enoic acid methyl ester (6.43 g, 83%) as a mixture of two isomers in ratio 2:1. Palladium 10% on carbon (0.3 g) was added to a stirred solution of the above alkenes (6.43 g, 9.36 mmol) in THF/IMS (100 ml, 1:1). Hydrogenation was carried out for 1 h. The solution was filtered through Celite and evaporated. The product was purified by chromatography eluting with petrol/ether (20:1) to give a colourless oil, (*R*)-2-[(*R*)-3-benzyloxy-1-(*tert*-butyl-dimethylsilanyloxy)propyl]hexacosanoic acid methyl ester **46** (6.30 g, 98%), $[\alpha]_D^{28}$ −6.20 (*c* 0.79, $CHCl_3$) {Found $(M+Na)^+$: 711.5701, $C_{43}H_{80}NaO_4Si$ requires: 711.5718} as a colourless oil. This showed δ_H: 7.37–7.27 (5H, m), 4.50 (2H, s), 4.10 (1H, br.q, *J* 5.1 Hz), 3.67 (3H, s), 3.58–3.54 (2H, m), 2.55 (1H, ddd, *J* 3.8, 6.6, 10.4 Hz), 1.80 (2H, br.q, *J* 6.6 Hz), 1.66–1.16 (46H, m, v. br.), 0.89 (3H, t, *J* 7.0 Hz), 0.86 (9H, s), 0.05 (3H, s), 0.04 (3H, s); δ_C: 174.7, 138.5, 128.3, 127.6, 127.5, 72.9, 70.7, 66.2, 52.0, 51.3, 33.7, 31.9, 29.7(v. br.), 29.65, 29.58, 29.45, 29.36, 27.9, 27.2, 25.7, 22.7, 17.9, 14.1, −4.6, −4.9; ν_{max}: 2925, 2854, 1740, 1664, 1464, 1361, 1254, 1195, 1168, 1102 cm^{-1}.

*3.1.30. (R)-2-[(R)-1-(tert-Butyldimethylsilanyloxy)-3-hydroxypropyl] hexacosanoic acid methyl ester **48**.* Palladium 10% on carbon (1.5 g) was added to a stirred solution of (*R*)-2-[(*R*)-3-benzyloxy-1-(*tert*-butyldimethylsilanyloxy)propyl]tetracosanoic acid methyl ester **46** (13.55 g, 19.72 mmol) in ethyl acetate (100 ml) and hydrogenated for 3 days. The solution was filtered through Celite and the evaporated. Chromatography eluting with petrol/ether (2:1) gave a white solid, (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-3-hydroxypropyl]hexacosanoic acid methyl ester **48** (11.18 g, 95%), mp 35–37 °C, $[\alpha]_D^{22}$ −0.97 (*c* 0.86, $CHCl_3$) {Found $(M+Na)^+$: 621.5220, $C_{36}H_{74}NaO_4Si$ requires: 621.5249}. This showed δ_H: 4.15–4.12 (1H, m), 3.83–3.72 (2H, m), 3.70 (3H, s), 2.64 (1H, ddd, *J* 3.8, 6.3, 10.1 Hz), 1.90 (1H, br s), 1.80–1.74 (2H, m), 1.64–1.45 (10H, m), 1.35–1.12 (36H, m), 0.91–0.87 (12H, m, including a singlet at δ 0.88), 0.11 (3H, s), 0.07 (3H, s); δ_C: 174.7, 72.1, 59.53, 51.6, 51.0, 36.2, 32.4, 30.2(v. br.), 30.16, 30.15, 30.13, 30.1, 29.9, 29.8, 28.5, 27.6, 26.0, 23.1, 18.2, 14.4, −4.4, −4.7; ν_{max}: 3449, 2924, 2854, 1741, 1465, 1361, 1255, 1196, 1167, 1094 cm^{-1}.

*3.1.31. (R)-2-[(R)-1-(tert-Butyldimethylsilanyloxy)-3-oxopropyl]hexacosanoic acid methyl ester **49**.* Ester **48** (7.20 g, 12.06 mmol) in dichloromethane (50 ml) was added in portions at rt to a stirred solution of PCC (6.50 g, 30.15 mmol) in dichloromethane (400 ml). After 2 h, ether (300 ml) was added and filtered through silica. The solvent was evaporated. Chromatography eluting with petrol/ether (4:1) gave a colourless oil, (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-3-oxopropyl]hexacosanoic acid methyl ester **49** (6.48 g, 90%), $[\alpha]_D^{28}$ −4.42 (*c* 1.29, $CHCl_3$) {Found $[M+H]^+$: 597.5245, $C_{36}H_{73}O_4Si$ requires: 597.5273}. This showed δ_H: 9.81 (1H, dd, *J* 1.6, 2.7 Hz), 4.43 (1H, dt, *J* 4.7, 6.0 Hz), 3.69 (3H, s), 2.66 (1H, ddd, *J* 1.6, 4.7, 6.3 Hz), 2.61 (1H, ddd, *J* 2.7, 6.3, 8.8 Hz), 2.59 (1H, ddd, *J* 4.1, 6.3, 10.4 Hz), 1.61–1.26 (46H, m, v. br.), 0.90 (3H, t, *J* 6.6 Hz), 0.86 (9H, s), 0.08 (3H, s), 0.07 (3H, s); δ_C: 201.3, 174.0, 68.8, 52.3, 51.5, 48.1, 31.9, 29.7(v. br.), 29.66, 29.62, 29.54, 29.5, 29.4, 29.3, 27.8, 27.0, 25.6, 22.7, 17.9, 14.1, −4.6, −4.9; ν_{max}: 2925, 2854, 1736, 1465, 1362, 1255, 1196, 1168, 1098 cm^{-1}.

*3.1.32. (R)-2-[(R)-15-Bromo-1-(tert-butyldimethylsilanyloxy)-pentadecyl]hexacosanoic acid methyl ester **51**.* Lithium bis(trimethylsilyl)amide (11.32 ml, 12.00 mmol) was added to a stirred solution of ester **49** (3.50 g, 6.15 mmol) and sulfone **50** (4.22 g, 9.23 mmol) (see Supplementary data) in dry THF (100 ml) at −12 °C under nitrogen. The reaction was stirred at rt for 3 h then quenched with satd aq ammonium chloride (100 ml), extracted with petrol/ether (1:1, 3×150 ml), dried and the solvent evaporated. Chromatography eluting with petrol/ether (10:1) gave a colourless oil, (*R*)-2-[(*E*/*Z*)-(*R*)-15-bromo-1-(*tert*-butyldimethylsilanyloxy)pentadec-3-enyl]hexacosanoic acid methyl ester (4.19 g, 82%), as a 2:1 mixture of two isomers. Palladium 10% on carbon (1 g) was added to a stirred solution of the above alkenes (4.19 g, 5.06 mmol) in THF (50 ml) and ethanol (50 ml). Hydrogenation was carried out 3 h. The solution was filtered through Celite and the solvent was evaporated. Chromatography eluting with petrol/ether (20:1) gave a colourless oil, (*R*)-2-[(*R*)-15-bromo-1-(*tert*-butyldimethylsilanyloxy)pentadecyl]hexacosanoic acid methyl ester **51** (3.88 g, 92%), $[\alpha]_D^{26}$ −7.2 (*c* 0.68, $CHCl_3$) {Found $(M+Na)^+$: 851.6275, $C_{48}H_{97}BrNaO_3Si$ requires: 851.6283}. This showed δ_H: 3.92–3.90 (1H, m), 3.66 (3H, s), 3.41 (2H, t, *J* 6.9 Hz), 2.53 (1H, ddd, *J* 3.8, 7.0, 10.7 Hz), 1.86 (2H, quintet, *J* 6.9 Hz), 1.59–1.54 (2H, m), 1.53–1.35 (7H, m), 1.34–1.10 (61H, m), 0.87–0.76 (12H, including a triplet at δ 0.89, *J* 6.9 Hz and a singlet at δ 0.87), 0.05 (3H, s), 0.03 (3H, s); δ_C: 175.1, 73.2, 51.5, 51.9, 33.9, 33.6, 32.8, 31.9, 29.8, 29.7, 29.6, 29.4, 29.37, 28.8, 28.2, 27.2, 27.5, 25.7, 23.6, 22.7, 19.4, 18.0, 14.1, −4.4, −4.9, ν_{max}: 2924, 2854, 1741, 1464, 1361,1254, 1194, 1167, 1075, 836 cm^{-1}.

3.1.33. (R)-2-[(R)-1-(tert-Butyldimethylsilanyloxy)-15-(5-phenyl-5H-tetrazol-1-ylsulfanyl)pentadecyl]hexacosanoic acid methyl ester. Ester **51** (3.80 g, 4.58 mmol), anhydrous potassium carbonate (1.33 g, 9.61 mmol) and acetone (100 ml) were stirred vigorously for 18 h at rt. Water (200 ml) was added and the mixture was extracted with dichloromethane (1×200 ml, 2×100 ml). The combined organic phases were washed with brine (2×200 ml), dried and evaporated. Chromatography eluting with petrol/ether (4:1) gave a colourless oil, (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-15-(5-phenyl-5*H*-tetrazol-1-ylsulfanyl)pentadecyl]hexacosanoic acid methyl ester (3.64 g, 86%), $[\alpha]_D^{26}$ −5.9 (*c* 0.91, $CHCl_3$) {Found $(M+Na)^+$: 949.7295, $C_{55}H_{102}N_4NaO_3SSi$ requires: 949.7334}. This showed δ_H: 7.61–7.52 (5H, m), 3.93–3.89 (1H, m), 3.66 (3H, s), 3.40 (2H, t, *J* 7.3 Hz), 2.53 (1H, ddd, *J* 10.7, 6.9, 3.5 Hz), 1.83 (2H, quintet, *J* 7.6 Hz), 1.65–1.11 (70H, m), 0.93–0.82 (12H, m, including a triplet at δ 0.89, *J* 6.7 Hz, and a singlet at δ 0.87), 0.04 (3H, s), 0.02 (3H, s); δ_C: 175.1, 154.5, 133.7, 130.0, 129.7, 123.8, 73.1, 51.5, 51.2, 33.6, 33.3, 31.9, 29.8, 29.7 (v. br.), 29.6, 29.4, 29.3, 29.0, 28.8, 28.2, 27.8, 27.5, 25.7, 23.6, 22.7, 17.9, 14.1, −4.4, −5.0; ν_{max}: 2924, 2854, 1739, 1599, 1501, 1464, 1386, 1250, 1167, 1074, 837, 776, 760, 694 cm^{-1}.

3.1.34. (R)-2-[(R)-1-Hydroxy-15-(5-phenyl-5H-tetrazol-1-ylsulfanyl)pentadecyl]hexacosanoic acid methyl ester. The above ester

(3.64 g, 3.93 mmol) was dissolved in dry THF (25 ml) in a dry polyethylene vial under argon at rt and stirred. Pyridine (1.5 ml) and HF.pyridine (3 ml) were added and the mixture was stirred for 17 h at 45 °C. The reaction was diluted with petrol/ether (1:1, 100 ml) and neutralized by pouring into satd aq $NaHCO_3$ until no more carbon dioxide was liberated. The mixture was extracted and the aqueous layer was re-extracted with petrol/ether (1:1, 2×100 ml). The combined organic layers were washed with brine, dried and evaporated. Chromatography eluting with petrol/ether (5:2) gave a white solid, (*R*)-2-[(*R*)-1-hydroxy-15-(5-phenyl-5*H*-tetrazol-1-ylsulfanyl)pentadecyl]hexacosanoic acid methyl ester (2.70 g, 84%), $[\alpha]_D^{16}$ +3.4 (*c* 1.15, $CHCl_3$), mp 63–65 °C {Found $(M+Na)^+$: 835.6437, $C_{49}H_{88}N_4O_3SNa$ requires: 835.6469}. This showed δ_H: 7.61–7.52 (5H, m), 3.71 (3H, s), 3.69–3.63 (1H, br m), 3.40 (2H, t, *J* 7.6 Hz,), 2.44 (2H, dt, *J* 5.4, 8.8 Hz), 1.82 (2H, quintet, *J* 7.3 Hz), 1.75–1.68 (1H, m), 1.62–1.55 (1H, m), 1.51–1.38 (5H, m), 1.36–1.10 (63H, br m) 0.88 (3H, t, *J* 6.6 Hz); δ_C: 176.2, 154.5, 133.7, 130.0, 129.7, 123.8, 72.3, 51.5, 50.9, 35.7, 33.3, 31.9, 29.7(v. br.), 29.6, 29.54, 29.5, 29.4, 29.3, 29.0, 28.99, 28.6, 27.4, 25.7, 22.7, 14.1; $\nu_{max:}$ 3490, 2919, 1719, 1597, 1501, 1464, 1378, 1295, 1280, 1240, 1191, 1178, 1132 cm^{-1}.

3.1.35. (R)-2-[(R)-1-Acetoxy-15-(5-phenyl-5H-tetrazol-1-ylsulfanyl)-pentadecyl]hexacosanoic acid methyl ester. A mixture of acetic anhydride (34 ml) and anhydrous pyridine (34 ml) was added to a stirred solution of the (*R*)-2-[(*R*)-1-hydroxy-15-(5-phenyl-5*H*-tetrazol-1-yl-sulfanyl)pentadecyl]hexacosanoic acid methyl ester (2.63 g, 3.25 mmol) in dry toluene (80 ml) at rt. After 18 h, it was diluted with toluene (40 ml) and the solvent was evaporated under reduced pressure to give a solid. Chromatography eluting with petrol/ether (5:1) gave a white solid, (*R*)-2-[(*R*)-1-acetoxy-15-(5-phenyl-5*H*-tetrazol-1-ylsulfanyl)pentadecyl]hexacosanoic acid methyl ester (2.31 g, 83%), $[\alpha]_D^{17}$ +6.6 (*c* 1.20, $CHCl_3$), mp 51–53 °C {Found $(M+Na)^+$: 877.6554, $C_{51}H_{90}N_4O_4SNa$ requires: 877.6575}. This showed δ_H: 7.61–7.52 (5H, m), 5.09 (1H, ddd, *J* 3.8, 7.0, 10.8 Hz), 3.68 (3H, s), 3.40 (2H, t, *J* 7.6 Hz), 2.62 (1H, ddd, *J* 4.4, 7.0, 10.7 Hz), 2.03 (3H, s), 1.82 (2H, quintet, *J* 7.3 Hz), 1.56–1.49 (1H, m), 1.44 (3H, br pent., *J* 7.6 Hz), 1.38–1.09 (66H, br m), 0.89 (3H, t, *J* 7.0 Hz); δ_C: 173.6, 170.4, 156.3, 130.0, 129.7 (v. br.), 123.8, 74.1, 51.5, 49.6, 33.3, 31.9, 31.7, 29.7, 29.6, 29.5, 29.4, 29.04, 29.0, 28.6, 28.1, 27.4, 25.0, 22.7, 21.0, 14.1; ν_{max}: 2922, 2853, 1743, 1598, 1501, 1466, 1385, 1238, 1166, 1074, 1017 cm^{-1}.

3.1.36. (R)-2-[(R)-1-Acetoxy-15-(5-phenyl-5H-tetrazol-1-sulfonyl)pentadecyl]hexacosanoic acid methyl ester ***52****.* *m*-Chloroperbenzoic acid (1.85 g, 5.43 mmol) in dichloromethane (40 ml) was added at 0 °C to (*R*)-2-[(*R*)-1-acetoxy-15-(5-phenyl-5*H*-tetrazol-1-ylsulfanyl)pentadecyl]hexacosanoic acid methyl ester (2.28 g, 2.68 mmol) and $NaHCO_3$ (1.02 g, 12.20 mmol) in dichloromethane (40 ml) and stirred at rt for 20 h. The mixture was quenched by addition of a satd aq $NaHCO_3$ (50 ml) and extracted with dichloromethane (1×100 ml, 3×30 ml). The combined organic phases were washed with water (100 ml), dried and the solvent evaporated. Chromatography eluting with petrol/ether (5:1) gave a white solid, (*R*)-2-[(*R*)-1-acetoxy-15-(5-phenyl-5*H*-tetrazol-1-sulfonyl)pentadecyl]hexacosanoic acid methyl ester **52** (1.94 g, 82%), $[\alpha]_D^{18}$ +10.6 (*c* 0.83, $CHCl_3$) {Found $(M+Na)^+$: 909.6448, $C_{51}H_{90}N_4O_6SNa$ requires: 909.6473}. This showed δ_H: 7.71–7.67 (2H, m), 7.65–7.56 (3H, m), 5.08 (1H, ddd, *J* 4.1, 6.9, 10.7 Hz), 3.73 (2H, distorted t, *J* 8.2 Hz), 3.68 (3H, s), 2.62 (1H, ddd, *J* 4.4, 7.0, 11.1 Hz), 2.03 (3H, s), 1.95 (2H, br quintet, *J* 7.9 Hz), 1.69–1.56 (3H, m), 1.55–1.41 (4H, m), 1.39–1.09 (63H, br m), 0.88 (3H, t, *J* 6.6 Hz); δ_C: 173.6, 170.3, 153.5, 133.1, 131.4, 129.7, 125.1, 74.1, 56.0, 51.5, 49.6, 31.9, 31.7, 29.7 (v. br.), 29.6, 29.5, 29.4, 29.3, 29.1, 28.9, 28.1, 27.4, 24.9, 22.6, 21.9, 21.0, 14.1; ν_{max}: 3439, 2972, 2498, 1739, 1593, 1499, 1470, 1407, 1374, 1348, 1303, 1245, 1137, 1099, 1022 cm^{-1}.

3.1.37. (R)-2-((R)-1-Acetoxy-16-{(1R,2S)-2-[(19S,20S)-19-(tert-butyldimethylsilanyloxy)-20-methyloctatria-contyl]-cyclopropyl}octadecyl)hexacosanoic acid methyl ester ***53*** *(R=SiMe$_2$Bu^t).* Ester **52** (0.82 g, 0.92 mmol) was dissolved in dry THF (15 ml) and a solution of aldehyde **25** (0.69 g, 0.92 mmol) in dry THF (10 ml) was added at rt. This solution was cooled to −12 °C and lithium bis-(trimethylsilyl) amide (1.4 ml, 1.48 mmol, 1.06 M) was added. The solution was allowed to reach rt and stirred for 2 h. Ether (25 ml) and satd aq ammonium chloride (30 ml) were added. The organic phase was separated and the water layer was washed with petrol/ether (20:1, 3×100 ml). The combined organic layers were dried and the solvent was evaporated. Chromatography eluting with petrol/ether (20:1) gave a colourless oil, (*R*)-2-((*R*)-1-acetoxy-16-{(1*R*,2*S*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}hexadec-15-enyl)-hexacosanoic acid methyl ester (0.94 g, 72%) as a 4:1 mixture of isomers. Dipotassium azodicarboxylate (2.0 g, 10.31 mmol) was added to a stirred solution of the above alkenes (870 mg, 0.62 mmol) in THF (25 ml) and methanol (5 ml) at 5 °C. Half of a solution of glacial acetic acid (5 ml) and THF (2 ml) was added dropwise at 5 °C. The mixture was stirred at rt for 2 h, then the other half was then added and stirred overnight. Dipotassium azodicarboxylate (2.0 g) and then glacial acetic acid (5 ml) were added and stirred overnight. This mixture was added slowly to satd aq ammonium chloride, extracted with petrol/ether (1:1, 3×80 ml,) and the combined organic layers were washed with water (50 ml) and evaporated. The procedure was repeated. Chromatography eluting with petrol/ether (20:1) gave a white semi-solid, (*R*)-2-((*R*)-1-acetoxy-16-{(1*R*,2*S*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]-cyclopropyl}octadecyl)hexacosanoic acid methyl ester **53** (R=SiMe$_2$Bu^t) (790 mg, 91%), $[\alpha]_D^{23}$ −6.8 (*c* 0.31, $CHCl_3$), {Found $(M+Na)^+$: 1432.3752, $C_{93}H_{184}NaO_5Si$ requires: 1432.3805}. This showed δ_H: 5.10 (1H, dt, *J* 3.8, 7.9 Hz), 3.69 (3H, s), 3.52–3.49 (1H, m), 2.63 (1H, ddd, *J* 4.2, 6.8, 10.7 Hz), 2.04 (3H, s), 1.68–1.14 (146H, m, v. br.), 1.07–1.02 (1H, m), 0.91–0.88 (15H, m, including a s), 0.80 (3H, d, *J* 6.6 Hz), 0.69–0.65 (2H, m), 0.57 (1H, br.dt, *J* 4.1, 8.2 Hz), 0.04 (3H, s), 0.03 (3H, s), −0.32 (1H, br.q, *J* 5.4 Hz); δ_C: 173.6, 170.3, 75.9, 74.1, 51.5, 49.6, 37.7, 33.6, 32.5, 31.9, 31.7, 30.2, 30.0, 29.9, 29.7(v. br.), 29.7, 29.6, 29.5, 29.4, 29.4, 29.4, 28.7, 28.1, 27.7, 27.5, 26.0, 25.9, 25.0, 22.7, 21.0, 18.2, 15.8, 14.4, 14.1, 10.9, −4.2, −.4; ν_{max}: 2924, 2853, 1747, 1465, 1372, 1236 cm^{-1}.

3.1.38. (R)-2-((R)-1-Acetoxy-16-{(1S,2R)-2-[(19S,20S)-19-(tert-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}-octadecyl)hexacosanoic acid methyl ester ***55*** *(R=SiMe$_2$Bu^t).* Ester **52** (0.93 g, 1.04 mmol) was dissolved in dry THF (15 ml) and a solution of (1*S*,2*R*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropanecarbaldehyde (0.78 g, 1.04 mmol) in dry THF (10 ml) was added at rt. This solution was cooled to −12 °C and lithium bis(trimethylsilyl) amide (1.5 ml, 1.59 mmol, 1.06 M) was added, then allowed to reach rt and stirred for 2 h. Ether (25 ml) and satd aq ammonium chloride (30 ml) were added. The organic phase was separated and water layer was extracted with petrol/ether (20:1, 3×100 ml). The combined organic layers were dried and the solvent was evaporated. Chromatography eluting with petrol/ether (20:1) gave a colourless oil, (*R*)-2-((*R*)-1-acetoxy-16-{(1*S*,2*R*)-2-[(19*S*,20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}hexadec-15-enyl)hexacosanoic acid methyl ester (1.29 g, 88%) as a 4:1 mixture of two isomers. Dipotassium azo-dicarboxylate (3.0 g, 15.46 mmol) was added to

a stirred solution of the mixture (1.06 g, 0.81 mmol) in THF (20 ml) and methanol (5 ml) at 5 °C. Half of a solution of glacial acetic acid (5 ml) and THF (2 ml) was added dropwise at 5 °C and the mixture was stirred at rt for 2 h. The other half was added and the mixture was stirred overnight. Dipotassium azo-dicarboxylate (2.50 g) and then glacial acetic acid (2 ml) were added and stirred again overnight. This mixture was slowly added to satd aq ammonium chloride and extracted with petrol/ether (1:1, 3×80 ml,) and the combined organic layers were washed with water (50 ml) and the solvent was evaporated. The procedure was repeated. Chromatography eluting with petrol/ether (20:1) gave a white semi-solid, (*R*)-2-((*R*)-1-acetoxy-16-{(1*S*,2*R*)-2-[(19*S*, 20*S*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}octadecyl)-hexacosanoic acid methyl ester **55** (R=$SiMe_2Bu^t$) (960 mg, 84%), $[\alpha]_D^{23}$ −3.6 (*c* 0.58, $CHCl_3$) {Found $(M+Na)^+$: 1432.3763, $C_{93}H_{184}NaO_5Si$ requires: 1432.3805}, which showed essentially identical NMR and IR spectra to those of **53** (R=$SiMe_2Bu^t$) above.

*3.1.39. (R)-2-((R)-1-Acetoxy-16-{(1R,2S)-2-[(19S,20S)-19-hydroxy-20-methyloctatriacontyl]cyclopropyl}octadecyl)hexacosanoic acid methyl ester **53** (R=H).* Ester **53** (R=$SiMe_2Bu^t$) (880 mg, 0.62 mmol) was dissolved in dry THF (12 ml) in a dry polyethylene vial under argon at rt and stirred. Pyridine (0.5 ml) and HF.pyridine (1.0 ml) were added and the mixture was stirred for 17 h at 40 °C, then diluted with petrol/ether (1:1, 70 ml,) and neutralized with satd aq $NaHCO_3$. The mixture was extracted and the aqueous layer was re-extracted with petrol/ether (1:1, 2××50 ml). The combined organic layers were washed with brine, dried and evaporated. Chromatography eluting with petrol/ether (5:2) gave a white semi-solid, (*R*)-2-((*R*)-1-acetoxy-16-{(1*R*,2*S*)-2-[(19*S*,20*S*)-19-hydroxy-20-methyloctatriacontyl]cyclopropyl}octadecyl)hexacosanoic acid methyl ester **53** (R=H) (580 mg, 73%), $[\alpha]_D^{19}$ −1.9 (*c* 0.91, $CHCl_3$), mp 40–42 °C {Found $(M+Na)^+$: 1318.2785, $C_{87}H_{170}NaO_4$ requires: 1318.2940}. This showed δ_H: 5.08 (1H, br.dt, *J* 3.8, 7.9 Hz), 3.69 (3H, s), 3.51–3.48 (1H, m), 2.62 (1H, ddd, *J* 4.3, 6.8, 10.7 Hz), 2.04 (3H, s), 1.66–1.12 (151H, m, v. br.), 0.90 (3H, t, *J* 6.9 Hz), 0.86 (3H, d, *J* 7.0 Hz), 0.67–0.64 (2H, m), 0.57 (1H, br. dt, *J* 4.1, 8.2 Hz), - 0.32 (1H, br. q, *J* 5.4 Hz); δ_C: 173.7, 170.3, 75.2, 74.1, 51.5, 49.6, 38.2, 34.5, 33.4, 31.9, 31.7, 30.2, 27.0, 29.8, 29.7(v. br.), 29.66, 29.57, 29.47, 29.44, 29.40, 29.36, 28.7, 28.1, 27.5, 27.4, 26.3, 25.0, 22.7, 21.0, 15.8, 14.1, 13.6, 10.9; ν_{max}: 3427, 2918, 2849, 1745, 1469, 1373, 1237 cm^{-1}.

*3.1.40. (R)-2-((R)-1-Acetoxy-16-{(1S,2R)-2-[(19S,20S)-19-hydroxy-20-methyloctatriacontyl]cyclopropyl}octadecyl)hexacosanoic acid methyl ester **55** (**R**=**H**).* Ester **55** (R=$SiMe_2Bu^t$) (880 mg, 0.62 mmol) was stirred in dry THF (15 ml) in a dry polyethylene vial under argon at rt. Pyridine (0.5 ml) and HF.pyridine (1.0 ml) were added and the mixture was stirred for 17 h at 40 °C. The reaction was diluted with petrol/ether (1:1, 70 ml) and neutralized with satd aq $NaHCO_3$. The mixture was separated and the aqueous layer was re-extracted with petrol/ether (1:1, 2×50 ml). The combined organic layers were washed with brine, dried and the solvent was evaporated. Chromatography eluting with petrol/ether (5:1) gave a white solid, (*R*)-2-((*R*)-1-acetoxy-16-{(1*S*,2*R*)-2-[(19*S*,20*S*)-19-hydroxy-20-methyloctatriacontyl]cyclopropyl}octadecyl)hexacosanoic acid methyl ester **55** (R=H) (780 mg, 96%), $[\alpha]_D^{23}$ −2.8 (*c* 0.88, $CHCl_3$), mp 47–49 °C {Found $(M+Na)^+$: 1318.2886, $C_{87}H_{170}NaO_5$ requires: 1318.2940}. This showed an essentially identical NMR spectrum to that for **53** (R=H) above.

*3.1.41. (R)-2-{(R)-1-Hydroxy-16-[(1R,2S)-2-((19S,20S)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **54**.* Lithium hydroxide monohydrate (68 mg, 1.62 mmol) was added to ester **53** (R=H) (70 mg, 0.054 mmol) stirred in THF (5 ml), methanol (0.5 ml) and water (0.5 ml) at rt After 18 h at 45 °C, it was cooled to rt and petrol and ether (1:1, 10 ml) were added and the mixture acidified to pH 1 by addition of 5% HCl. Further petrol/ether (1:1, 10 ml) was added and extracted. The aq layer was re-extracted with petrol/ether (1:1, 2×10 ml). The combined organic layers were washed with water (5 ml), dried and evaporated. Chromatography eluting with petrol/ethyl acetate (3:1) gave a white solid, (*R*)-2-{(R)-1-hydroxy-16-[(1R,2S)-2-((19S,20S)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **54** (57 mg, 85%), $[\alpha]_D^{20}$ −0.5 (*c* 0.97, $CHCl_3$), mp 73–74 °C {Found $(M+Na)^+$: 1262.2618, $C_{84}H_{166}NaO_4$ requires: 1262.2678}. This showed δ_H: 3.74–3.70 (1H, m), 3.53–3.50 (1H, m), 2.46 (1H, dt, *J* 8.8, 5.4 Hz), 1.77–1.60 (1H, m), 1.67–1.12 (149H, m), 0.89 (6H, t, *J* 7.0 Hz), 0.87 (3H, d, *J* 7.0 Hz), 0.68–0.64 (2H, m), 0.57 (1H, br.dt, *J* 4.1, 8.2 Hz), - 0.32 (1H, br.q, *J* 5.4 Hz); δ_C: 178.4, 75.4, 72.1, 50.7, 38.1, 35.6, 34.4, 33.3, 31.9, 30.2, 29.9, 29.7(v. br.), 29.65, 29.61, 29.59, 29.55, 29.51, 29.43, 29.36, 28.7, 27.4, 27.3, 26.3, 25.7, 22.7, 15.8, 14.1, 13.6, 10.9; ν_{max}: 3333, 2917, 2851, 1719, 1519 cm^{-1}.

*3.1.42. (R)-2-{(R)-1-Hydroxy-16-[(1S,2R)-2-((19S,20S)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]-hexadecyl}hexacosanoic acid **56**.* Lithium hydroxide monohydrate (67 mg, 1.60 mmol) was added at rt with stirring to ester **55** (R=H) (70 mg, 0.05 mmol) in THF (5 ml), methanol (0.5 ml) and water (0.5 ml). The mixture was stirred at 45 °C for 18 h, then cooled to rt and petrol/ether (1:1, 10 ml) was added and the mixture was acidified to pH 1 by addition of 5% HCl. Further petrol/ether (1:1, 10 ml) was added and extracted. The aq layer was re-extracted with petrol/ether (1:1, 2×10 ml). The combined organic layers were washed with water (5 ml), dried and evaporated. Chromatography eluting with 3:1 petrol/ethyl acetate gave a white solid, (*R*)-2-{(*R*)-1-hydroxy-16-[(1*S*,2*R*)-2-((19*S*,20*S*)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **56** (60 mg, 86%), $[\alpha]_D^{22}$ +0.05 (*c* 0.86, $CHCl_3$), mp 58–60 °C, {Found $(M+Na)^+$: 1262.2752$C_{84}H_{166}NaO_4$ requires: 1262.2678}, which showed an essentially identical NMR spectrum to that above.

*3.1.43. 2,2-Dimethyl-propionic acid 10-{(1R,2S)-2-[(19R,20R)-19-(tert-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}decyl ester **58**.* 2,2-Dimethylpropionic acid 9-(2-phenyl-2*H*-pentazol-1-sulfonyl)nonyl ester (**57**) (prepared as for **12**; see Supplementary data) (0.95 g, 2.18 mmol) was dissolved in dry THF (20 ml) and a solution of (1*R*,2*S*)-aldehyde **22** (1.3 g, 1.74 mmol) in dry THF (20 ml) was added at rt. This solution was cooled to −12 °C and lithium bis(trimethylsilyl) amide (2.96 ml, 3.14 mmol, 1.06 M) was added at between −12 and −4 °C. The solution was allowed to reach rt and stirred for 2 h. Petrol/ether (1:1, 50 ml) and satd aq ammonium chloride (100 ml) were added. The organic phase was separated and the water layer was extracted with petrol/ether (1:1, 2×40 ml). The combined organic layers were dried and the solvent was evaporated. Chromatography eluting with petrol/ether (33:1) gave a colourless oil, 2,2-dimethyl-propionic acid (*E*/*Z*)-10-{(1*R*,2*S*)-2-[(19*R*, 20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatria-contyl]cyclopropyl}-dec-9-enyl ester (1.45 g, 87%) as a mixture of two isomers in ratio 5.9:1 {Found $(M+Na)^+$: 979.9184, $C_{63}H_{124}NaO_3Si$ requires: 979.9212}. The alkene (1.4 g, 1.46 mmol) and 2,4,6-triisopropylbenzenesulfonylhydrazine (1.53 g, 5.13 mmol) were stirred in dry THF (40 ml) at 45 °C for 24 h. Further TPBSH (0.52 g, 1.75 mmol) was added and stirred at 45 °C for another 24 h. The mixture was diluted with petrol/ether (1:2, 100 ml) and aq sodium hydroxide (30 ml, 2%) was added and extracted. The aqueous layer was re-extracted with petrol/ether (1:2, 2×25 ml) and the combined organic layers were washed with water (100 ml), dried and evaporated. Chromatography eluting with petrol/ether (33:1) gave a colourless oil, 2,2-dimethylpropionic acid 10-{(1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-

methyloctatriacontyl]cyclopropyl}decyl ester **58** (1.3 g, 93%), $[\alpha]_D^{19}$ +5.6 (*c* 1.3, $CHCl_3$) {Found $(M+Na)^+$: 981.9332, $C_{63}H_{126}NaO_3Si$ requires: 981.9368}. This showed δ_H: 4.05 (2H, t, *J* 6.6 Hz), 3.51 (1H, dt, *J* 3.5, 6.3 Hz), 1.66–1.60 (2H, m), 1.50–1.12 (86H, m, v. br.), 1.21 (9H, s), 1.10–1.02 (1H, m), 0.91–0.88 (12H, s and t, *J* 6.7 Hz), 0.81 (3H, d, *J* 6.6 Hz), 0.67–0.63 (2H, m), 0.58 (1H, br.dt, *J* 4.1, 8.2 Hz), 0.04 (3H, s), 0.03 (3H, s), −0.32 (1H, br.q, *J* 5.1 Hz); δ_C: 178.6, 75.9, 64.5, 38.7, 37.7, 33.6, 32.5, 31.9, 30.2, 30.0, 29.9, 29.75, 29.7(v. br.), 29.57, 29.52, 29.4, 29.3, 28.7, 28.6, 27.7, 27.2, 26.0, 25.9, 22.7, 18.2, 15.8, 14.4, 14.1, 10.9, −4.2, −4.4; ν_{max}: 2925, 2854, 1733, 1464, 1284, 1253, 1155 cm^{-1}.

*3.1.44. 10-{(1R,2S)-2-[(19R,20R)-19-(tert-Butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}decanal **59**.*

(i) The ester **58** (1.2 g, 1.25 mmol) in dry THF (10 ml) was added dropwise over 15 min to a suspension of lithium aluminium hydride (71 mg, 1.88 mmol, 1.5 mol equiv) in THF (20 ml) at 0 °C under nitrogen, then refluxed for 1 h. Satd aq sodium sulfate decahydrate was added at 0 °C until a white precipitate had formed. THF (25 ml) was added and the mixture was stirred at rt for 30 min, filtered through silica and the solvent was evaporated. Chromatography eluting with petrol/ether (2:1) gave a colourless oil, 10-{(1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}decan-1-ol (0.75 g, 69%), $[\alpha]_D^{25}$ +5.9 (*c* 1.16, $CHCl_3$) {Found $(M-H)^+$: 873.8788, $C_{58}H_{117}O_2Si$ requires: 873.8817}. This showed δ_H: 3.65 (2H, t, *J* 6.6 Hz), 3.51 (1H, dt, *J* 3.5, 6.3 Hz), 1.60–1.55 (2H, m), 1.51–1.14 (86H, m, v. br.), 1.09–1.02 (1H, m), 0.91–0.88 (12H, s and t, *J* 6.9 Hz), 0.80 (3H, d, *J* 6.7 Hz), 0.68–0.63 (2H, m), 0.57 (1H, br.dt, *J* 4.1, 8.2 Hz), 0.04 (3H, s), 0.03 (3H, s), −0.32 (1H, br.q, *J* 5.4 Hz); δ_C: 75.9, 63.1, 37.7, 33.6, 32.8, 32.5, 31.9, 30.2, 30.0, 29.9, 29.7(v. br.), 29.62, 29.6, 29.5, 29.4, 28.7, 27.7, 26.0, 25.9, 25.8, 22.7, 18.2, 15.8, 14.4, 14.1, 10.9, −.2, −4.4; ν_{max}: 3332, 2924, 2854, 1465, 1253, 1058 cm^{-1}.

(ii) A solution of the above alcohol (0.62 g, 0.73 mmol) in dichloromethane (20 ml) was added with stirring to PCC (0.38 g, 1.77 mmol) in dichloromethane (60 ml) at rt. After 2 h it was diluted with ether (50 ml), filtered through a bed of silica and the solvent was evaporated. Chromatography eluting with petrol/ether (15:1) gave a colourless oil, 10-{(1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}decanal **59** (0.59 g, 95%), $[\alpha]_D^{24}$ +5.1 (*c* 0.9, $CHCl_3$) {Found $(M+Na)^+$: 895.8638, $C_{58}H_{116}NaO_2Si$ requires: 895.8637}. This showed δ_H: 9.77 (1H, t, *J* 1.9 Hz), 3.52–3.48 (1H, m), 2.43 (2H, dt, *J* 1.9, 7.4 Hz), 1.64 (2H, quintet, *J* 7.3 Hz), 1.51–1.14 (84H, m, v. br.), 1.09–1.01 (1H, m), 0.90–0.87 (12H, m, including a s), 0.80 (3H, d, *J* 6.7 Hz), 0.67–0.64 (2H, m), 0.57 (1H, br.dt, *J* 4.1, 8.2 Hz), 0.04 (3H, s), 0.03 (3H, s), −0.32 (1H, br.q, *J* 5.4 Hz); δ_C: 202.9, 75.9, 43.9, 37.7, 33.6, 32.5, 31.9, 30.2, 30.2, 30.0, 29.9, 29.7(v. br.), 29.64, 29.62, 29.44, 29.36, 29.2, 28.7, 28.7, 27.7, 26.0, 25.9, 22.7, 22.1, 18.2, 15.8, 15.8, 14.4, 14.1, 10.9, −4.2, −4.4; ν_{max}: 2932, 2854, 1731, 1465, 1361, 1253, 1074 cm^{-1}.

*3.1.45. (R)-2-((R)-1-Acetoxy-16-{(1R,2S)-2-[(19R,20R)-19-(tert-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}-hexadecyl)hexacosanoic acid methyl ester **60**.* Ester **39** (0.54 g, 0.72 mmol) was dissolved in dry THF (30 ml) and a solution of (1*R*,2*S*)-aldehyde **59** (0.5 g, 0.57 mmol) in dry THF (10 ml) was added at rt After cooling to −12 °C lithium bis-(trimethylsilyl)amide (1.05 ml, 1.09 mmol, 1.06 M) was added. After stirring at rt for 2 h. Ether (25 ml) and satd aq ammonium chloride (30 ml) were added. The aqueous layer was extracted with petrol/ether (1:2, 2×40 ml). The combined organic layers were dried and evaporated. Chromatography eluting with petrol/ether (18:1) gave a colourless oil, (*R*)-2-((*E*/*Z*)-(*R*)-1-acetoxy-16-{(1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclo-propyl}hexadec-6-enyl)hexacosanoic acid methyl ester (0.45 g, 56%) as a 2:1 mixture of isomers, {Found $(M+Na)^+$: 1430.3699, $C_{93}H_{182}NaO_5Si$ requires: 1430.3649}. Dipotassium azodicarboxylate (2 g, 10.3 mmol) was added with stirring to the above alkenes (400 mg, 0.28 mmol) in THF (20 ml) and methanol (4 ml) at 5 °C. A solution of glacial acetic acid (2.5 ml) and THF (2.5 ml) was prepared and half of this solution was added at 5 °C dropwise and the mixture was stirred at rt for 2 h. The other half of the glacial acetic acid solution was added at rt and the mixture was stirred overnight. Dipotassium azodicarboxylate (1.5 g) was added and glacial acetic acid (2 ml) was added and stirred again overnight. This mixture was added slowly to satd aq ammonium chloride and extracted with petrol/ether (1:1, 3×80 ml) and the combined organic layers were washed with water (50 ml) and evaporated. The procedure was repeated. Chromatography eluting with petrol/ether (15:1) gave a white solid, (*R*)-2-((*R*)-1-acetoxy-16-{(1*R*,2*S*)-2-[(19*R*,20*R*)-19-(*tert*-butyldimethylsilanyloxy)-20-methyloctatriacontyl]cyclopropyl}hexadecyl)hexacosanoic acid methyl ester **60** (350 mg, 88%), mp 29–30 °C, $[\alpha]_D^{24}$ +7.9 (*c* 0.79, $CHCl_3$) {Found $(M+Na)^+$: 1432.3752, $C_{93}H_{184}NaO_5Si$ requires: 1432.3805}; ν_{max}: 2924, 2853, 1747, 1465, 1372, 1236, 1164, 1022 cm^{-1}. This showed an essentially identical NMR spectra to **53** (R=$SiMe_2Bu^t$) and **55** (R=$SiMe_2Bu^t$) above.

*3.1.46. (R)-2-{(R)-1-Acetoxy-16-[(1R,2S)-2-((19R,20R)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **61**.* The methyl ester **60** (300 mg, 0.21 mmol) was dissolved in dry THF (15 ml) in a dry polyethylene vial under argon at rt and stirred. Pyridine (0.3 ml) and HF.pyridine (1.2 ml) were added and the mixture was stirred for 17 h at 40 °C. The reaction was diluted with petrol/ether (1:1, 70 ml) and neutralized with satd aq $NaHCO_3$, then separated and the aqueous layer was re-extracted with petrol/ether (1:1, 2×50 ml). The combined organic layers were washed with brine, dried and evaporated. Chromatography eluting with petrol/ether (4:1) gave a white solid, (*R*)-2-{(*R*)-1-acetoxy-16-[(1*R*,2*S*)-2-((19*R*,20*R*)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **61** (260 mg, 94%), mp 47–48 °C, $[\alpha]_D^{21}$ +9.3 (*c* 0.95, $CHCl_3$) {Found $(M+Na)^+$: 1318.3003, $C_{87}H_{170}NaO_5$ requires: 1318.2940}; ν_{max}: 3449, 2918, 2850, 1743, 1470, 1374, 1238 cm^{-1}. This showed essentially identical NMR spectra to **53** (R=H) and **55** (R=H) above.

*3.1.47. (R)-2-{(R)-1-Hydroxy-16-[(1R,2S)-2-((19R,20R)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **62**.* Lithium hydroxide monohydrate (23 mg, 0.55 mmol) was added to ester **61** (24 mg, 0.019 mmol) stirred in THF (5 ml), methanol (0.5 ml) and water (0.4 ml) at rt, then heated to 45 °C for 18 h. After cooling to rt, petrol/ether (1:1, 10 ml) and then sat aq ammonium chloride (5 ml) were added and the mixture was acidified to pH 1 by addition of 5% HCl. Further petrol/ether (1:1, 10 ml) was added and extracted. The aq layer was re-extracted with petrol/ether (1:1, 2×10 ml). The combined organic layers were washed with water (5 ml), dried and the solvent evaporated. Chromatography eluting with petrol/ethyl acetate (3:1) gave a white solid, (*R*)-2-{(*R*)-1-hydroxy-16-[(1*R*,2*S*)-2-((19*R*,20*R*)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **62** (14 mg, 61%), mp 64–66 °C, $[\alpha]_D^{25}$ +9.1 (*c* 0.6, $CHCl_3$) {Found $(M+Na)^+$: 1262.16, $C_{84}H_{166}NaO_4$ requires: 1262.27; Found: C, 81.4; H, 13.3, $C_{84}H_{166}O_4$ requires: C, 81.35; H, 13.49}; ν_{max}: 3331, 2921, 2852, 1688, 1463, 1377, 1201 cm^{-1}. This showed essentially identical NMR spectra to **54** and **56** above.

*3.1.48. (R)-2-{(R)-1-Acetoxy-16-[(1R,2S)-2-((R)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **65**.* Ester **61** (150 mg, 0.12 mmol) in dichloromethane (5 ml) was added in portions to PCC (62.5 mg, 0.29 mmol) stirred in

dichloromethane (25 ml) at rt After 3 h, it was diluted with ether (40 ml), filtered through silica and the solvent evaporated. Chromatography eluting with petrol/ether (6:1) gave a white solid, (*R*)-2-{(*R*)-1-acetoxy-16-[(1*R*,2*S*)-2-((*R*)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **65** (150 mg, 100%), mp 49–50 °C, $[\alpha]_D^{20}$ +3.0 (*c* 0.7, $CHCl_3$) {Found $(M+Na)^+$: 1316.2779, $C_{87}H_{168}NaO_5$ requires: 1316.2784}. This showed δ_H: 5.09 (1H, dt, *J* 3.8, 7.9 Hz), 3.69 (3H, s), 2.62 (1H, ddd, *J* 4.4, 6.9, 10.7 Hz), 2.50 (1H, sext, *J* 6.8 Hz), 2.43 (1H, dt, *J* 14.7, 7.3 Hz), 2.40 (1H, dt, *J* 14.7, 7.3 Hz), 2.03 (3H, s), 1.68–1.14 (144H, m, v. br.), 1.05 (3H, d, *J* 7.0 Hz), 0.89 (6H, t, *J* 7.0 Hz), 0.68–0.64 (2H, m), 0.57 (1H, br.dt, *J* 4.1, 8.2 Hz), - 0.32 (1H, br.q, *J* 5.0 Hz); δ_C: 215.1, 173.6, 170.3, 74.1, 51.5, 49.6, 46.3, 41.1, 33.1, 31.9, 31.7, 30.2, 29.8, 29.7(v. br.), 29.65, 29.63, 29.60, 29.56, 29.51, 29.49, 29.46, 29.44, 29.40, 29.36, 28.7, 28.1, 27.5, 27.3, 25.0, 23.7, 22.7, 21.0, 16.4, 15.8, 14.1, 10.9; ν_{max}: 2919, 2850, 1740, 1708, 1471, 1376, 1241, 1166, 1020 cm^{-1}.

*3.1.49. (R)-2-{(R)-1-Acetoxy-16-[(1R,2S)-2-((S)-20-methyl-19-oxooctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **63**.* The ester **53** (150 mg, 0.116 mmol) in dichloromethane (5 ml) was added in portions to a stirred solution of PCC (74.8 mg, 0.347 mmol) in dichloromethane (10 ml) at rt. The mixture was stirred for 3 h then diluted with ether (10 ml), filtered through silica and evaporated. Chromatography eluting with petrol/ether (5:1) gave a white solid, (*R*)-2-{(*R*)-1-acetoxy-16-[(1*R*,2*S*)-2-((*S*)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **63** (134 mg, 89%), mp 49–50 °C $[\alpha]_D^{20}$ +7.3 (*c* 0.86, $CHCl_3$) {Found $(M+Na)^+$: 1316.2784, $C_{87}H_{168}NaO_5$ requires: 1316.2784}, which showed an essentially identical NMR spectrum to that of its diastereoisomer **65** above.

*3.1.50. (R)-2-{(R)-1-Acetoxy-16-[(1S,2R)-2-((S)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **64**.* Ester **55** (150 mg, 0.116 mmol) was dissolved in dichloromethane (5 ml) and added in portions to a stirred solution of PCC (74.8 mg, 0.347 mmol) in dichloromethane (10 ml) at rt. The mixture was stirred for 3 h then diluted with ether (40 ml) and filtered through silica. The solvent was evaporated. Chromatography eluting with petrol/ether (6:1) gave a white solid, (*R*)-2-{(*R*)-1-acetoxy-16-[(1*S*,2*R*)-2-((*S*)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid methyl ester **64** (135 mg, 90%), mp 59–60 °C, $[\alpha]_D^{20}$ +8.1 (*c* 0.94, $CHCl_3$) {Found $(M+Na)^+$: 1316.2780, $C_{87}H_{168}NaO_5$ requires: 1316.2784}. This showed an essentially identical NMR spectrum to that of its diastereoisomers **65** and **63** above.

*3.1.51. (R)-2-{(R)-1-Hydroxy-16-[(1R,2S)-2-((R/S)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **66**.*

(i) Lithium hydroxide monohydrate (68 mg, 1.62 mmol) was added to a stirred solution of ester **65** (70 mg, 0.054 mmol) in THF (12 ml), methanol (1.2 ml) and water (1 ml) at rt. The mixture was stirred at 45 °C for 18 h. It was cooled to rt and a mixture of petrol/ether (1:1, 10 ml) and then sat aq ammonium chloride (10 ml) was added and the mixture was acidified to pH 1 by dropwise addition of 5% HCl. Further petrol/ether (1:1, 20 ml) was added and extracted. The aq layer was re-extracted with petrol/ether (1:1, 2×20 ml). The combined organic layers were washed with water (15 ml), dried and the solvent was evaporated. Chromatography eluting with petrol/ethyl acetate (7:2) gave a white solid, (*R*)-2-{(*R*)-1-hydroxy-16-[(1*R*,2*S*)-2-((*R/S*)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]exadecyl}hexacosanoic acid **66** (54 mg, 81%), mp 70–72 °C, $[\alpha]_D^{26}$ +4.4 (*c* 1.02, $CHCl_3$) {Found $(M+Na)^+$: 1260.12, $C_{84}H_{164}NaO_4$ requires: 1260.25; Found: C, 81.94; H, 13.24, $C_{84}H_{164}O_4$ requires: C, 81.48; H, 13.35}. This showed δ_H: 3.74–3.70 (1H, m), 2.51 (1H, sext, *J* 6.9 Hz), 2.46 (1H, dt, *J* 8.8, 5.4 Hz), 2.43 (1H, dt, *J* 14.8, 7.3 Hz), 2.40 (1H, dt, *J* 14.8, 7.3 Hz), 1.75–1.12 (144H, m, v. br.), 1.05 (3H, d, *J* 7.0 Hz), 0.89 (6H, t, *J* 7.0 Hz), 0.69–0.64 (2H, m), 0.57 (1H, br.dt, *J* 4.1, 8.2 Hz), - 0.32 (1H, br.q, *J* 5.4 Hz); δ_C: 215.4, 179.6, 72.1, 50.8, 46.3, 41.1, 35.5, 33.0, 31.9, 30.2, 29.7(v. br.), 29.66, 29.60, 29.52, 29.50, 29.46, 29.43, 29.36, 29.33, 28.7, 27.3, 25.7, 23.7, 22.7, 16.4, 15.8, 14.1, 10.9; ν_{max}: 3285, 2919, 2850, 1707, 1470, 1377, 1204, 1019 cm^{-1}.

(ii) Lithium hydroxide monohydrate (64.26 mg, 1.53 mmol) was added to ester **63** (66 mg, 0.051 mmol) stirred in THF (5 ml), methanol (0.5 ml) and water (0.5 ml) at rt. The mixture was stirred at 45 °C for 18 h, cooled to rt and petrol/ether (1:1, 10 ml) was added and acidified to pH 1 by adding 5% HCl. Further petrol/ethyl acetate (5:2, 20 ml) was added and extracted. The aq layer was re-extracted with petrol/ethyl acetate (5:2, 4×20 ml). The combined organic layers were washed with water (15 ml), dried and evaporated. Chromatography eluting with petrol/ethyl acetate (7:2) gave a white solid, the acid **66** (55 mg, 87%), $[\alpha]_D^{20}$ +4.9 (*c* 0.70, $CHCl_3$), mp 71–73 °C {Found $(M+Na)^+$: 1260.2501, $C_{84}H_{164}NaO_4$ requires: 1260.2522}, which showed an identical NMR spectrum to that above.

*3.1.52. (R)-2-{(R)-1-Hydroxy-16-[(1S,2R)-2-((R/S)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **67**.* Lithium hydroxide monohydrate (48.7 mg, 1.16 mmol) was added to ester **64** (50 mg, 0.039 mmol) stirred in THF (5 ml), methanol (0.5 ml) and water (0.5 ml) at rt. After 18 h at 45 °C, it was cooled to rt, petrol/ethyl acetate (5:2, 10 ml) was added and it was acidified to pH 1 by addition of 5% HCl. The aq layer was re-extracted with petrol/ethyl acetate (5:2, 5×20 ml). The combined organic layers were washed with water (15 ml), dried and evaporated. Chromatography eluting with petrol/ethyl acetate (7:2) gave a white solid, (*R*)-2-{(*R*)-1-hydroxy-16-[(1*S*,2*R*)-2-((*R/S*)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **67** (41 mg, 87%), $[\alpha]_D^{23}$ +3.5 (*c* 0.59, $CHCl_3$), mpmp 73–75 °C {Found $(M+Na)^+$: 1260.2478, $C_{84}H_{164}NaO_4$ requires: 1260.2522}. This showed an essentially identical NMR to that of **66** above.

*3.1.53. ((R)-2-((R)-1-acetoxy-16-{(1R,2S)-2-[(19S,20S)-20-methyl-19-(tetrahydropyran-2-yloxy)octatriacontyl]cyclopropyl}hexadecyl)hexacosanoic acid methyl ester **68**.* Pyridinium *p*-toluene sulfonate (24 mg, 0.095 mmol) in dry dichloromethane (0.5 ml) was added with stirring to ester **53** (R=H) (254 mg, 0.196 mmol) and freshly distilled dihydro-2*H*-pyran (0.2 ml, 2.206 mmol) in dry dichloromethane (5 ml) at rt under nitrogen. After 1.5 h, the reaction was quenched with a satd aq $NaHCO_3$ (10 ml), extracted with dichloromethane (3×30 ml) and the combined organic layers were dried and evaporated. Chromatography, eluting with petrol/ether (5:2) with a few drops of Et_3N gave a white semi-solid, ((*R*)-2-((*R*)-1-acetoxy-16-{(1*R*,2*S*)-2-[(19*S*,20*S*)-20-methyl-19-(tetrahydropyran-2-yloxy)octatriacontyl]cyclopropyl}hexadecyl)hexacosanoic acid methyl ester as a mixture of diastereoisomers **68** (230 mg, 86%). {Found $(M+Na)^+$: 1402.3516, $C_{92}H_{178}NaO_6$ requires: 1402.3466}. This showed δ_H: 5.09 (2H, ddd, *J* 3.8, 7.9, 10.8 Hz), 4.66 (1H, br., t, *J* 3.15 Hz), 4.62 (1H, br., t, *J* 2.5 Hz), 3.95–3.69 (2H, m), 3.69 (6H, s), 3.51–3.43 (4H, m), 2.62 (2H, ddd, *J* 4.4, 7.0, 10.7 Hz), 2.04 (6H, s), 1.85–1.80 (2H, m), 1.73–1.05 (304H, m), 0.88 (12H, t, *J* 7.25 Hz), 0.85 (6H, d, *J* 6.9 Hz), 0.68–0.62 (4H, m), 0.57 (2H, br., dt, *J* 4.1, 8.2 Hz), −0.33 (2H, br., q, *J* 5.1 Hz); ν_{max}: 2849, 1747, 1467, 1372, 1236, 1024, 721 cm^{-1}.

*3.1.54. (R)-2-((R)-1-Hydroxy-16-{(1R,2S)-2-[(19S,20S)-20-methyl-19-(tetrahydropyran-2-yloxy)octatriacontyl]cyclopropyl}hexadecyl)hexacosanoic acid **69**.* Lithium hydroxide monohydrate (106 mg, 2.47 mmol) was added to a stirred solution of ester **68**

(225 mg, 0.149 mmol) in THF (10 ml), methanol (1.5 ml) and water (1.0 ml) at rt. The mixture was stirred at 45 °C for 16 h, then cooled to rt and diluted with petrol/ethyl acetate (5:2, 25 ml) and acidified with 2 M HCl to pH 2–3. The aqueous layer was washed with petrol/ethyl acetate (5:2, 3×20 ml). The combined organic layers were washed with water (20 ml), dried and evaporated. Chromatography eluting with 7:2 petrol/ethyl acetate gave a white semi-solid, (*R*)-2-((*R*)-1-hydroxy-16-{(1*R*,2*S*)-2-[(19*S*,20*S*)-20-methyl-19-(tetrahydropyran-2-yloxy)octatriacontyl]cyclopropyl}hexadecyl)hexacosanoic acid **69** as a mixture of diastereoisomers (130 mg, 60%) {Found $(M+Na)^+$: 1346.3253; $C_{89}H_{174}NaO_5$ requires: 1346.3319}. This showed δ_H: 4.67 (1H, br t, *J* 3.15 Hz), 4.64 (1H br.t, *J* 2.85 Hz), 3.97–3.88 (2H, m), 3.74–3.70 (2H, m), 3.52–3.43 (4H, m,), 2.47 (2H, br.pent, *J* 4.75 Hz), 1.87–1.79 (4H, m), 1.77–1.05 (306H, m), 0.89 (12H, t, *J* 6.65), 0.84 (6H, d, *J* 6.65 Hz), 0.69–0.62 (4H, m), 0.57 (2H, br.dt, *J* 4.1, 8.55 Hz), −0.33 (2H, br.q, *J* 5.05 Hz); ν_{max}: 2920, 2851, 1682, 1465, 1378, 1216, 1132, 1077, 1024, 869 cm^{-1}.

3.1.55. (R)-2-((R)-1-(tert-Butyldimethylsilanyloxy)-16-{(1R,2S)-2-[(19S,20S)-20-methyl-19-(tetrahydropyran-2-yloxy)octatriacontyl]-cyclopropyl}-hexadecyl)hexacosanoic acid ***70***. Imidazole (65 mg, 0.96 mmol) was added with stirring to hydroxyacid **69** (125 mg, 0.096 mmol) in dry DMF (1 ml) and toluene (1.5 ml) at rt, followed by the addition of *tert*-butyldimethylsilylchloride (143 mg, 0.955 mmol) and 4-dimethylaminopyridine (10 mg, 0.082 mmol), then heated to 70 °C for 18 h. The solvent was removed under high vacuum and the residue diluted with petrol/ethyl acetate (1:1) (30 ml) and satd aq $NaHCO_3$ (5 ml); the organic layer was separated and the aqueous layer was re-extracted with petrol/ethyl acetate (3×15 ml). The combined organic layers were washed with water, dried and evaporated. The residue was dissolved in THF (10 ml), water (1.5 ml), and methanol (1.5 ml) and potassium carbonate (150 mg) were added, stirred at 45 °C for 6 h, then diluted with petrol/ethyl acetate (10:1, 20 ml) and water (2 ml) and acidified to pH 2 with potassium hydrogen sulfate. The organic layer was separated and the aqueous layer was re-extracted with petrol/ethyl acetate (2×20 ml). The combined organic layers were washed with water, dried and evaporated. Chromatography eluting with petrol/ethyl acetate (20:1) gave a white semi-solid, (*R*)-2-((*R*)-1-(*tert*-butyldimethylsilanyloxy)-16-{(1*R*,2*S*)-2-[(19*S*, 20*S*)-20-methyl-19-(tetrahydropyran-2-yloxy)octatriacontyl]cyclopropyl}hexadecyl)-hexacosanoic acid **70** as a mixture of diastereoisomers (104 mg, 76%) {Found $(M+Na)^+$: 1460.4118, $C_{95}H_{188}NaO_5$ requires: 1460.4064}. This showed δ_H: 4.66 (1H, br., t, *J* 3.15 Hz), 4.63 (1H, br., t, *J* 4.45 Hz), 3.86–3.94 (2H, m), 3.86–3.82 (2H, m) 3.52–3.43 (4H, m), 2.53 (2H, ddd, *J* 3.15, 5.95, 9.15 Hz), 1.89–1.79 (4H, m), 1.75–1.03 (304H, m), 0.93 (18H, s), 0.89 (12H, t, *J* 6.65 Hz), 0.85 (6H, d, *J* 6.9 Hz), 0.68–0.62 (4H, m), 0.56 (2H, br. dt., *J* 4.1, 8.15 Hz), 0.15 (6H, s), 0.13 (6H, s), -0.33 (2H, br.q, *J* 5.05 Hz); ν_{max}: 2924, 1708, 1466, 1255, 1024, 836, 775 cm^{-1}.

3.1.56. (R)-2-{(R)-1-(tert-Butyldimethylsilanyloxy)-16-[(1R,2S)-2-((S)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}-hexacosanoic acid ***71***.

(i) Pyridinium-*p*-toluenesulfonate (100 mg, 0.40 mmol) was added to (*R*)-2-((*R*)-1-(*tert*-butyldimethyl-silanyloxy)-16-{(1*R*, 2*S*)-2-[(19*S*,20*S*)-20-methyl-19-(tetrahydropyran-2-yloxy)-octatriacontyl]cycloprop-yl}hexadecyl)hexacosanoic acid **70** (100 mg, 0.07 mmol) in THF (4 ml), MeOH (0.5 ml) and H_2O (0.2 ml) and stirred at 47 °C for 7 h. Satd aq sodium bicarbonate (3 drops) was added and the product was extracted with petrol/ethyl acetate (3×15 ml, 1:1). The combined organic layers were dried and evaporated. Chromatography eluting with 10:1 petrol/ethyl acetate gave (*R*)-2-{(*R*)-1-(*tert*-butyldimethyl-silanyloxy)-16-[(1*R*,2*S*)-2-((19*S*,20*S*)-19-hydroxy-20-methyloctatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid as a white semi-solid (60 mg, 0.044 mmol, 60%), $[\alpha]_D^{25}$ −2.06 (*c* 0.68, $CHCl_3$) {Found $(M+Na)^+$: 1376.3600, $C_{90}H_{180}NaO_4Si$ requires: 1376.3543}. This showed δ_H: 3.87 (1H, br.q, *J* 5.4 Hz) 3.53–3.48 (1H, br.pent, *J* 3.75 Hz), 2.53 (1H, br.pent, *J* 5.05 Hz), 1.70–1.60 (1H, m), 1.59–1.52 (2H, m), 1.51–1.09 (146H, m), 0.91 (9H, s), 0.89 (6H, t, *J* 7 Hz), 0.86 (3H, d, *J* 7.0 Hz), 0.68–0.62 (2H, m), 0.57 (1H, br. dt, *J* 4.05, 8.15 Hz), 0.12 (3H, s), 0.10 (3H, s), −0.33 (1H, br. q, *J* 5.05 Hz); δ_C: 177.11, 75.23, 73.56, 50.66, 38.16, 35.03, 34.48, 33.36, 31.93, 30.22, 29.96, 29.76, 29.71, 29.66, 29.65, 29.58, 29.52, 29.5, 29.42, 29.36, 29.06, 28.72, 27.53, 27.42, 26.27, 25.73, 24.65, 22.69, 17.94, 15.77, 14.10, 13.57, 10.91, −4.31, −4.92; ν_{max}: 3400, 3058, 2923, 2852, 2682, 1709, 1465, 1362, 1254, 1077, 1006, 970, 939, 908, 836, 811, 775 cm^{-1}.

(ii) The above acid (60 mg, 0.044 mmol) in dichloromethane (2 ml) was added in portions to a stirred solution of PCC (50 mg, 0.232 mmol) in dichloromethane (2 ml) at rt. After 2 h, it was diluted with petrol/ethyl acetate (20 ml, 10:1), filtered over Celite and evaporated. Chromatography (10:1 petrol/ethyl acetate) gave (*R*)-2-{(*R*)-1-(*tert*-butyldimethylsilanyloxy)-16-[(1*R*,2*S*)-2-((*S*)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]-hexadecyl}hexacosanoic acid **71** as a white semi-solid (44 mg, 74%), $[\alpha]_D^{25}$ +5.18 (*c* 0.83, $CHCl_3$) {Found $(M+Na)^+$: 1374.3387, $C_{90}H_{178}NaO_4Si$ requires: 1374.3367}; δ_H: 3.87 (1H, br., q, *J* 5.05 Hz), 2.51 (2H, m), 2.42 (2H, dt, *J* 2.2, 7.25 Hz), 1.72–1.60 (2H, m), 1.59–1.53 (4H, m), 1.51–1.10 (139H, m) 1.06 (3H, d, *J* 7.0 Hz) 0.92 (9H, s), 0.89 (6H, t, *J* 7.0 Hz), 0.69–0.63 (2H, m), 0.57 (1H, br., dt, *J* 4.1, 8.5 Hz), 0.12 (3H, s), 0.10 (3H, s), −0.33 (1H, br., q, *J* 5.05 Hz); δ_C: 215.18, 176.43, 73.63, 50.44, 46.34, 41.15, 35.34, 33.05, 31.94, 30.22, 29.69, 29.67, 29.63, 29.60, 29.55, 29.51, 29.49, 29.46, 29.41, 29.36, 29.33, 28.72, 27.48, 27.32, 25.73, 24.82, 23.71, 22.68, 17.93, 16.35, 15.76, 14.10, 10.91, −4.29, 4.92; ν_{max}: 2924, 2853, 1709, 1464, 1363, 1254, 1216, 1078, −939, 836, 760, 721, 667 cm^{-1}.

3.1.57. (R)-2-{(R)-1-Hydroxy-16-[(1R,2S)-2-((S)-20-methyl-19-oxo-octatriacontyl)cyclopropyl]hexadecyl}hexacosanoic acid ***72***. A dry polyethylene vial equipped with a rubber septum was charged with acid **71** (44 mg, 0.0325 mmol) and pyridine (100 μL) in dry THF (4 ml) and stirred at rt under nitrogen and hydrogen fluoride-pyridine complex (230 μL, 70:30) was added. After 13 h at 42 °C, it was diluted with petrol/ethyl acetate (10 ml, 1:1) and neutralized by pouring into satd aq sodium bicarbonate. The aqueous layer was re-extracted with petrol/ethyl acetate (3×15 ml, 1:1). The combined organic layers were washed with brine, dried and evaporated. Chromatography (7:2 petrol/ethyl acetate) gave a white solid, (*R*)-2-{(*R*)-1-hydroxy-16-[(1*R*,2*S*)-2-((*S*)-20-methyl-19-oxo-octa-triacontyl)cyclopropyl]hexadecyl}hexacosanoic acid **72** (33 mg, 83%), $[\alpha]_D^{26}$ +7.34 (*c*=0.79, $CHCl_3$), mp 66–68 °C {Found $(M+Na)^+$: 1260.2522, $C_{84}H_{164}NaO_4$ requires: 1260.2568}. This showed; δ_H: 3.72 (1H, br., pent, *J* 4.7 Hz), 2.52 (1H, q, *J* 6.6 Hz), 2.48 (1H, m), 2.42 (2H, dt, *J* 1.85, 7.25 Hz), 1.78–1.70 (1H, m), 1.67–1.60 (2H, m), 1.59–1.46 (6H, m), 1.4–1.10 (137H, m), 1.05 (3H, d, *J* 6.95 Hz), 0.89 (6H, t, *J* 7.25 Hz), 0.71–0.62 (2H, m), 0.56 (1H, br.dt, *J* 4.1, 8.5 Hz), −0.33 (1H, br.q, *J* 5.00 Hz); δ_C: 215.42, 179.80, 72.12, 50.86, 46.33, 41.15, 35.51, 33.04, 31.92, 30.23, 29.71, 29.66, 29.52, 29.50, 29.47, 29.43, 29.37, 29.33, 28.73, 27.33, 25.73, 23.73, 22.69, 16.35, 15.78, 14.11, 10.91, ν_{max}: 3284, 2919, 2850, 1708, 1465, 1377, 721 cm^{-1}.

Supplementary data

The supplementary data associated with this article can be found in the on-line version at doi:10.1016/j.tet.2009.09.099.

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