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The synthesis of methoxy and keto mycolic acids containing methyl-*trans*-cyclopropanes

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ABSTRACT

The syntheses of a number of methoxy and keto-mycolic acids containing an α-methyl-*trans*-cyclopropane unit and with chain lengths identical to those reported in major homologues in natural samples are reported.

1. Introduction

Mycolic acids, e.g., **1** (Fig. 1), are characteristic components of the cells of mycobacteria and of a number of related organisms, such as *Rhodococcus* and *Nocardia*, some of which are pathogenic to animals and humans.[1–6] Their presence is thought to be linked to the characteristic resistance of many such organisms to most current antibiotics and other chemotherapeutic agents.[7]

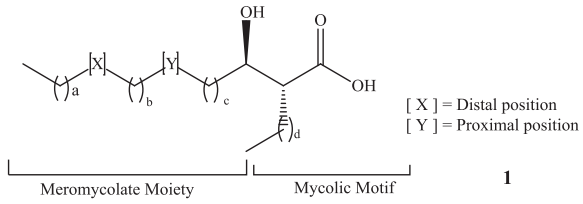

Fig. 1. A generalised mycolic acid structure.

The mycolic acids present as major constituents of the cell envelope of *Mycobacterium tuberculosis* can be divided into a number of main groups, including α-mycolic acids with two *cis*-cyclopropanes as X and Y, **2**, and methoxy-**3** and keto-mycolic acids **4** with one *cis*-cyclopropane.[5,6] In addition they include methoxy- and keto-mycolic acids in which there is a *trans*-cyclopropane substituted with a methyl group on the adjacent carbon distal from the hydroxy acid, **5** and **6** (Fig. 2). The 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.[8–12]

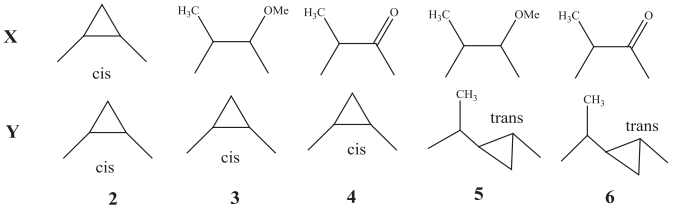

Fig. 2. Common combinations of X and Y in *M. tuberculosis* mycolic acids.

The presence of the β-hydroxy group and the relative configuration between it and the alkyl chain has been shown to be capable of altering the film molecular packing.[13,14] 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;[15] the same is true for the anti-tumour properties of mycolic acid derivatives.[16] The balance of α-mycolic acids **2**, methoxy-**3** and **5** and

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keto-mycolic acids, such as **4** and **6** is characteristic of specific bacteria;[5,6] in each case, each class of mycolic acid is present as a mixture of homologues. In the case of *M. tuberculosis*, the exact role of each type in the pathogenesis of disease remains to be confirmed, but the oxygenated mycolic acids have a particular influence on macrophage growth; strains lacking ketomycolates have a reduced ability to grow within THP-1 cells.[17,18] Moreover, the absence of keto and methoxy-mycolates leads to attenuation of *M. tuberculosis* in mice;[19] the vaccine strain *Mycobacterium bovis* BCG-Pasteur lacks methoxy-mycolates.[20–22] *M. tuberculosis* controls host innate immune activation through cyclopropane modification of a glycolipid effector molecule.[23–25] 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 macrophage inflammatory response.[26] The stereochemistry was shown to directly affect the interaction with host cells to affect innate immune activation both positively and negatively. Such MAs have a particular effect on the cell wall and therefore on the sensitivity of mycobacterial species to hydrophobic antibiotics.[27] The genes responsible for *trans*-cyclopropanation have been examined,[27,28] and cyclopropanation has been theoretically modelled.[29]

We have recently reported the synthesis of an α-mycolate of type **2**,[30] and of methoxy-mycolates of type **3** with either absolute stereochemistry at the *cis*-cyclopropane or α-methyl-β-methoxy fragment.[31] We have also reported the synthesis of meromycolate fragments containing the α-methyl-*trans*-cyclopropane unit present in mycobacterial wax esters, again in a variety of stereochemistries, and provided evidence that the relative stereochemistry of methyl and cyclopropane is as shown in **7**, since the cyclopropane region of the ^{1}H NMR spectrum of this stereoisomer matches that of the natural material, whereas that of an isomer with the opposite relative stereochemistry of methyl group and cyclopropane is quite different.[32] Moreover, at least in the case of wax esters derived by enzymatic Baeyer–Villiger reaction of ketomycolates, the absolute stereochemistry of this sub-unit appears to be as shown in **7**.[33] There is evidence that in most cases the methoxy and methyl groups of mycolic acids **3** and **5** are *S*,*S* and that the α-methyl ketone of ketomycolates is *S*, though it is not clear whether the stereochemistry is important for biological effect.[9,34,35] We have briefly reported syntheses of protected ketomycolates containing both α-methyl-*trans*- and *cis*-cyclopropane fragments, **6** and **4** that can be adjusted to produce a variety of absolute stereochemistries and chain lengths.[36] However, deprotection of these led to epimerisation at the methyl-position adjacent to the ketone. More recently, we have reported in full the synthesis of keto-MA containing *cis*-cyclo-propanes.[37] We now report in full the synthesis of both keto- and methoxy-MA containing an α-methyl-*trans*-cyclopropane fragment **7** (Fig. 3).

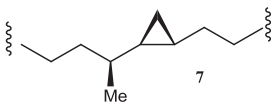
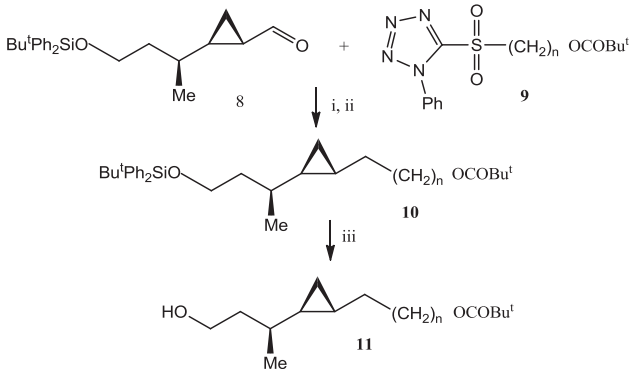


Fig. 3. A typical α-methyl-*trans*-cyclopropane fragment.

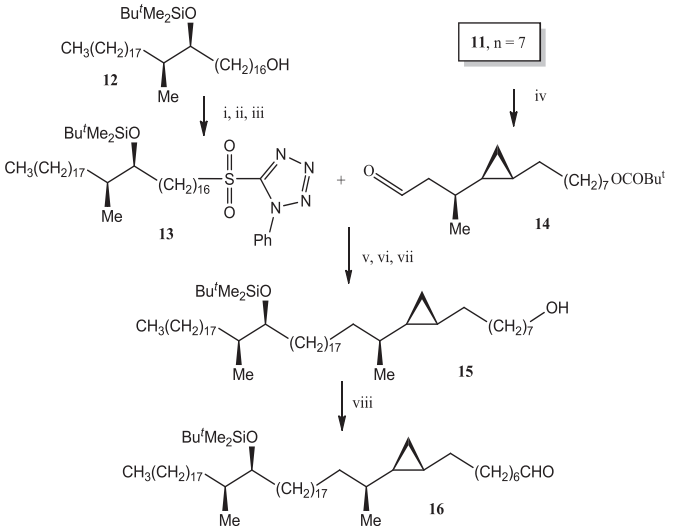
2. Results and discussion

As in other syntheses of mycolic acids, the molecules were constructed from three fragments, one the fragment containing group X, one group Y, the third the β-hydroxy acid part, and these were linked through modified Julia–Kocienski reactions, followed by hydrogenation of the derived mixture of *E*/*Z*-alkenes. The known cyclopropane **8**,[32,33] was first coupled to sulfone **9** (n=7) (prepared by a modification of a standard method; see Supplementary data) using lithium hexamethyldisilazide, then the derived mixture of alkenes was hydrogenated using 2,4,6-triisopropyl sulfonylhydrazide, to produce the chain extended ester **10** (n=7), $[\alpha]_D^{25}$ +7.61 (*c* 1.31, $CHCl_3$). This was deprotected to produce the alcohol **11** (n=7), $[\alpha]_D^{25}$ +16.05 (*c* 1.19, $CHCl_3$) (Scheme 1).



Scheme 1. (i) LiHMDS, THF, 69%; (ii) 2,4,6-triisopropyl sulfonylhydrazide, THF, 87%; (iii) tetra-*n*-butyl ammonium fluoride, THF, 91%.

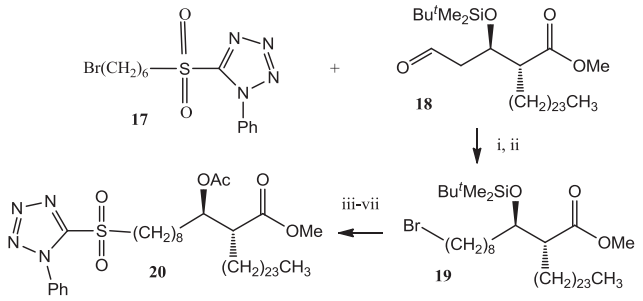
The alcohol was then converted into aldehyde **14**, which was coupled in the next step to the sulfone **13**, prepared in three standard steps from alcohol **12**. Reaction between the two compounds in the presence of lithium hexamethyldisilazide led to a 70% yield of an *E*/*Z*-mixture of alkenes, which was hydrogenated using di-imide to produce the meromycolate fragment **15** after partial deprotection. Oxidation of **15** led to the aldehyde **16**, ready for the final coupling to produce the complete carbon skeleton of the mycolic acid (Scheme 2).



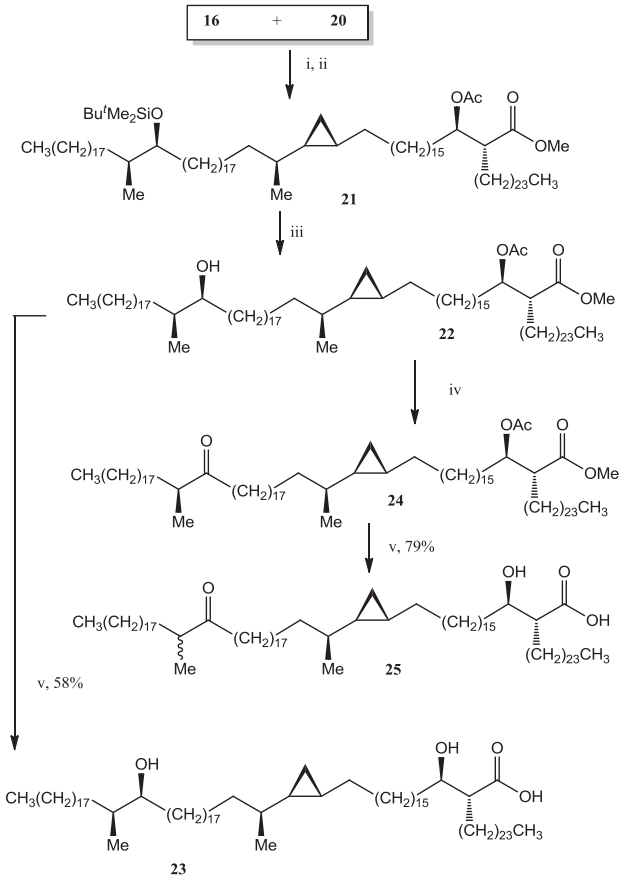
Scheme 2. (i) *N*-Bromosuccinimide, PPh_3, CH_2Cl_2, 91%; (ii) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3, acetone, THF, 95%; (iii) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS, THF, 82%. (iv) PCC, CH_2Cl_2, 91%; (v) LiHMDS, THF, 70%; (vi) KOOCN=NCOOK, AcOH/MeOH/THF, 75%; (vii) $LiAlH_4$, THF, 82%; (viii) PCC, CH_2Cl_2, 86%.

The final coupling required the sulfone **20**, prepared, as described earlier for different chain lengths, from aldehyde **18** (Scheme 3).

Coupling of **16** and **20** with base, followed by saturation of the derived alkenes led to the protected mycolic acid **21** (Scheme 4). Deprotection using HF-pyridine and pyridine, followed by lithium hydroxide produced the hydroxymycolic acid **23**, the first example of a synthetic hydroxy-MA containing a *trans*-cyclopropane.



Scheme 3. (i) LiHMDS, THF, 94%; (ii) H_2, Pd/C, 36%; (iii) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3, acetone, 79%; (iv) HF–pyridine, pyridine, THF, 81%; (v) acetic anhydride, pyridine, toluene, 84%; *m*-chloroperbenzoic acid, $NaHCO_3$, CH_2Cl_2, 88%.



Scheme 4. (i) LiHMDS, THF, 47%; (ii) KOOCN=NCOOK, AcOH/MeOH/THF, 75%; (iii) HF-pyridine, pyridine, THF, 74%; (iv) PCC, CH_2Cl_2, 83%; (v) LiOH·H_2O, MeOH/THF/H_2O.

Hydroxy-MA are relatively uncommon, though they have been observed in some organisms,[34] and are thought to be intermediates in the formation of keto-MA and methoxy-MA.[18,35]

Deprotection with HF-pyridine and pyridine followed by oxidation gave the protected keto-MA **24** as a single diastereoisomer.[32,33] This was fully characterised by ^1H and ^{13}C NMR.[38] The MALDI MS showed an $[M+Na]^+$ centred at 1302, matching a major *trans*-cyclopropane keto-mycolic acid in *M. tuberculosis*,[39] and some other mycobacteria,[40] and also a major peak in keto-mycolic acid isolated from *Mycobacterium avium*.[38] Deprotection of this using lithium hydroxide led to epimerisation adjacent to the ketone. The product **25** showed an $[\alpha]_D^{19}$ +4.74 (*c* 0.78, $CHCl_3$), corresponding to an $[M_D]$ of 61.6. The contribution to $[M_D]$ of the *S*-methylketone is known to be +44, that of the hydroxy acid +40. In related systems, the contribution from the methyl-*trans*-cyclopropane unit **7** is ca. +25.[32,33] The observed value of $[M_D]$ for **25** is therefore consistent with no contribution from the epimerized α-methyl ketone fragment.

In the same way, the aldehyde **26** was coupled to sulfone **27** and, through a series of similar reactions (see Supplementary data) was converted into the diastereomeric hydroxy-MA **28** and keto MA **29** (Fig. 4). Deprotection of **29**, [α] +3.0 (*c* 0.7, $CHCl_3$), with LiOH·H_2O, MeOH/THF/H_2O gave approximately the same mixture of epimers **25** as that derived from **24**. Thus the product showed identical NMR spectra and the specific rotation, $[\alpha]_D^{26}$ +5.3 (*c* 0.96, $CHCl_3$), was close to that above.

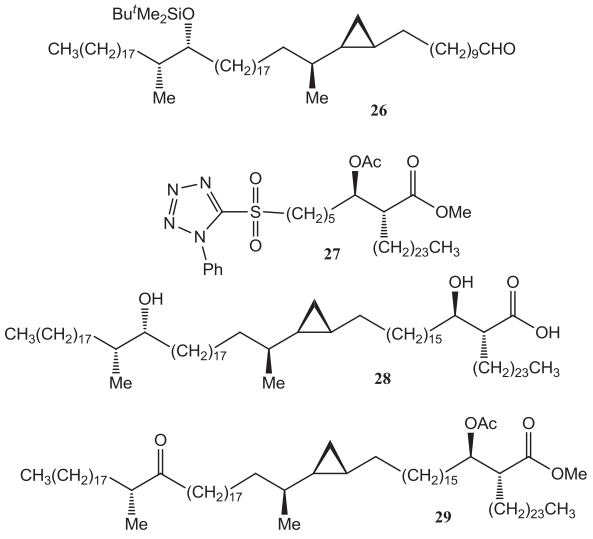
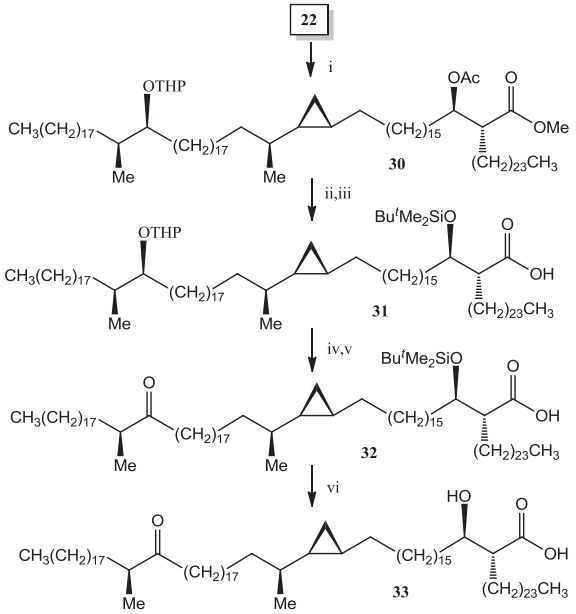


Fig. 4. Keto-mycolic acid **29** and precursors.

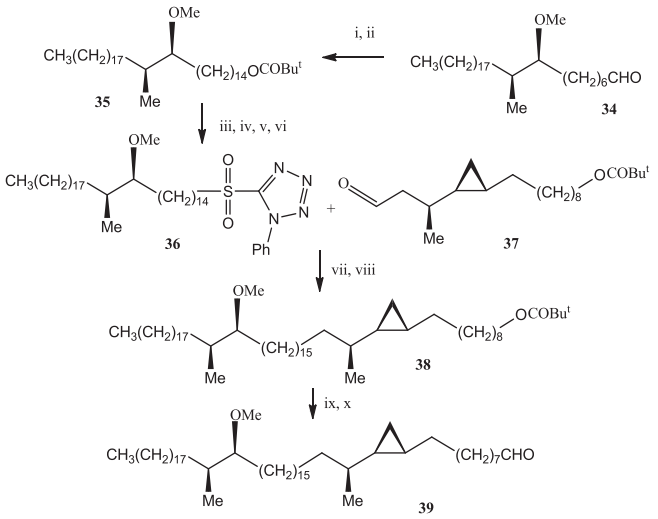
In order to obtain the keto-MA without epimerisation, the protecting group on the meromycolate HO-group was changed to tetrahydropyanyl and that on the β-hydroxy group to a silyl ether as in Scheme 5. After oxidation and hydrolysis of the ester, the β-silyloxy group could then be deprotected under acidic conditions, leaving the stereochemistry adjacent to the ketone unchanged.



Scheme 5. (i) Dihydropyran, H^+, CH_2Cl_2, 94%; (ii) LiOH·H_2O, MeOH/THF/H_2O, 45 °C, 90%; (iii) imidazole, DMF, toluene, TBDMSCl, 70 Co, K_2CO_3, MeOH/THF/H_2O, then $KHSO_4$, 84%; (iv) pyridinium *p*-toluene sulfonate, MeOH/THF/H_2O, 47 Co, 73%; (v) PCC, CH_2Cl_2, 88%; (vi) HF-pyridine, pyridine, THF, 84%.

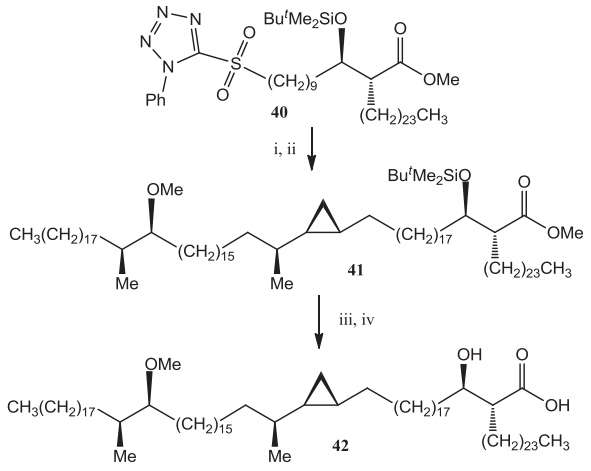
The product ketone **33** now had an $[\alpha]_D^{19}$ +10.55 (c 0.54, $CHCl_3$), corresponding to an $[M_D]$ of +137, with a predicted value, based on the figures above, of +109.

In order to prepare a *trans*-cyclopropane containing methoxy-MA, the fragment **34** was coupled to sulfone **9** (n=7) using LiHMDS, and the resultant alkenes were hydrogenated to provide the chain extended ester **35**. This was converted in four steps into the sulfone **36** and this in turn was coupled to the aldehyde **37** (prepared from **11** (n=8)). After saturation of the derived alkenes, deprotection and oxidation provided the aldehyde **39** (Scheme 6).



Scheme 6. (i) **9** (n=7), LiHMDS, THF, 81%; (ii) H_2, Pd/C, 88%; (iii) $LiAlH_4$, THF, 79%; (iv) *N*-bromosuccinimide, PPh_3, CH_2Cl_2, (v) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (vi) *m*-chloroperbenzoic acid, $NaHCO_3$, CH_2Cl_2, 89%; (vii) LiHMDS, THF, 54%; (viii) KOOCN=NCOOK, AcOH/MeOH/THF, 97%; (ix) $LiAlH_4$, THF, 72%; (x) PCC, CH_2Cl_2, 96%.

The sulfone fragment **40** with the required chain length was prepared from **18** using a similar method to that described before for **20** (Supplementary data). Finally, coupling of the **39** and **40** using LiHMDS, followed by hydrogenation of the mixture of alkenes produced, gave the protected methoxy-MA **41**, which could be deprotected to provide the free acid **42** (Scheme 7).



Scheme 7. (i) **39**, LiHMDS, THF, 28%, (ii) KOOCN=NCOOK, AcOH/MeOH/THF, 94%; (iii) HF-pyridine, pyridine, THF, 54%; (iv) $LiOH \cdot H_2O$, H_2O/THF/MeOH, 69%.

The acid **42** showed all the expected signals in both the proton and carbon NMR spectra. It gave a mass ion at 1318 ($M+Na^+$), which matched a major homologue of the *trans*-cyclopropane mycolic acid series in a sample of methoxy-mycolic acid from *M. tuberculosis*.[6,39,40] The $[\alpha]_D^{22}$ of −0.97 ($CHCl_3$, 0.468 μmol) corresponded to an $[M_D]$ of −12.6. The reported contribution to $[M_D]$ by the *S,S*-α-methyl-β-methoxy-fragment is around −45,[31] so the observed value is somewhat lower than expected on the basis of additive contributions.

The *trans*-cyclopropane mycolic acids described above have already been found to show interesting biological properties. In initial ELISA assays to compare the recognition of synthetic mycolic acids by antibodies in the serum of TB positive patients, the epimeric *trans*-cyclopropane keto-MA **25** gave stronger binding and somewhat better distinction between TB positive and TB negative serum samples than related synthetic *cis*-cyclo-propane keto-MA, though the response was somewhat lower than that to a mixture of natural mycolic acids from *M. tuberculosis*.[41] The methoxy-MA **42** gave higher signals in ELISA than the natural mixture, and was somewhat better at distinguishing TB+/TB−; related *cis*-methoxy-MAs were less effective.[41] In studies of mouse pulmonary inflammation in response to intratracheal treatments with mycolic acids, methoxy- and keto-MA containing *cis*-cyclopropanes caused solid to mild inflammatory responses, respectively. The *trans*-cyclopropane methoxy-MA **42** partially lost its inflammatory activity and keto-MA **25** exerted anti-inflammatory alternative activation of alveolar macrophages and counteracted *cis*-methoxy-MA induced airway inflammation.[42,43] These differential innate immune activities may point to a novel means for *M. tuberculosis* to steer host immune responses during infection while the anti-inflammatory property of **25** might be of significance in the therapeutics of inflammatory disorders.[44] Further studies of these effects are under way.

3. Experimental section

3.1. General

Chemicals used were obtained from commercial suppliers (Sigma, Aldrich, and Alfa Aeser) or prepared from them by the methods described. Solvents which were required to be dry, e.g., ether, tetrahydrofuran were dried over sodium wire and benzophenone under nitrogen, while dichloromethane and HMPA were dried over calcium hydride. All reagents and solvents used were of reagent grade unless otherwise stated. Silica gel (Merck 7736) and silica gel plates used for column chromatography and thin layer chromatography were obtained from Aldrich; separated components were detected using variously UV light, I_2 and phosphomolybdic acid solution in IMS followed by charring. Anhydrous magnesium sulfate was used to dry organic solutions. Infra-red (IR) spectra were carried out on a Perkin–Elmer 1600 FTIR spectrometer as liquid films or KBr disc (solids). Melting points were measured using a Gallenkamp melting point apparatus. NMR spectra were carried out on a Bruker AC250 or Advance 400 spectrometer. $[\alpha]_D$ values were recorded in $CHCl_3$ on a POLAAR 2001 optical activity polarimeter. Mass spectra were recorded on a Bruker matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS) values are given plus sodium to an accuracy of 2 d.p.

*3.1.1. 2,2-Dimethylpropionic acid 8-{(1S,2R)-2-[(S)-3-(tert-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octyl ester (**10**, n=7).* *trans*-(1*S*,2*R*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde **8**,[32,33] (2.66 g, 7.00 mmol) in dry THF (20 mL) was added at room temperature to 2,2-dimethylpropionic acid 7-(1-phenyl-1*H*-tetrazol-5-sulphonyl)-heptyl ester **9** (n=7) (3.71 g, 9.09 mmol) (see Supplementary data) in dry THF (30 mL). This solution was cooled to −12 °C and lithium bis(trimethylsilyl) amide (12.8 mL, 13.7 mmol, 1.06 M) was added at

between −12 and −4 °C. The mixture was allowed to reach rt and stirred for 2 h, then cooled to 0 °C and quenched with satd aq ammonium chloride (100 mL). The product was extracted with petrol/ether (1:1, 3×50 mL). The combined organic layers were washed with brine (100 mL), dried and evaporated to give an oil. Column chromatography eluting with petrol/ether (7:1) gave 2,2-dimethylpropionic acid 8-{(1*R*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methyl-propyl]cyclopropyl}oct-7-enyl ester (2.79 g, 69%), as a mixture of two isomers in ratio 2.6:1. The alkenes (2.40 g, 4.27 mmol) and 2,4,6-tri-isopropylbenzenesulphonyl hydrazide (5.11 g, 17.1 mmol) were stirred in dry THF (60 mL) at 40 °C for 18 h. Further TPBSH (2.61 g, 8.74 mmol) was added and stirred at 50 °C for 23 h. ^{1}H NMR spectroscopy showed that hydrogenation was complete. The mixture was diluted with petrol/ether (1:1, 200 mL) and aq sodium hydroxide solution (100 mL, 2%) was added and the organic layer was separated. The aqueous layer was re-extracted with petrol/ether (1:1, 2×60 mL) and the combined organic layers were washed with water (50 mL), dried and evaporated. Column chromatography eluting with petrol/ether (15:1) gave the title compound as a colourless oil, **10** (*n*=7) (2.1 g, 87%), $[\alpha]_D^{25}$ +7.61 (*c* 1.31, $CHCl_3$) [Found $(M+Na)^+$: 587.3886, $C_{36}H_{56}O_3Si+Na$ requires: 587.3896]. This showed δ_H (500 MHz, $CDCl_3$): 7.73–7.69 (4H, m), 7.46–7.38 (6H, m), 4.10 (2H, t, *J* 6.6 Hz), 3.80–3.73 (2H, m), 1.80–1.71 (1H, m), 1.66 (2H, br pent, *J* 6.5 Hz), 1.60–1.55 (1H, m), 1.38–1.22 (20H, br m including s at δ 1.24), 1.21–1.15 (1H, m), 1.12 (9H, s), 0.98–0.88 (4H, including s at δ 0.93), 0.46–0.40 (1H, m), 0.18–0.137 (2H, m), 0.12–0.09 (1H, m); δ_C (126 MHz, $CDCl_3$): 178.7, 135.6, 134.2, 129.5, 127.5, 64.4, 62.3, 40.2, 38.7, 34.8, 34.3, 29.52, 29.5, 29.2, 28.6, 27.2, 26.9, 25.9, 25.88, 19.8, 19.2, 18.6, 10.6; ν_{max}: 2920, 2850, 1730 cm^{-1}.

*3.1.2. 2,2-Dimethylpropionic acid 8-[(1S,2R)-2-((S)-3-hydroxy-1-methylpropyl)cyclopropyl]-octyl ester (**11**, n=7).* Tetra-*n*-butylammonium fluoride (4.78 mL, 4.78 mmol, 1 M in THF) was added with stirring to ester **10**, (*n*=7) (1.8 g, 3.2 mmol) in dry THF (30 mL) at 0 °C under argon. The mixture was allowed to reach room temperature, stirred for 18 h, diluted with petrol/ethyl acetate (1:1, 100 mL), cooled to 5 °C and quenched with satd aq ammonium chloride (50 mL). The water layer was re-extracted with petrol/ethyl acetate (1:1, 2×30 mL), the combined organic layers were washed with brine (75 mL), dried and the solvent evaporated. Column chromatography eluting with petrol/ethyl acetate (5:1, then 4:1) gave the title compound **11**, (*n*=7) (0.95 g, 91%), $[\alpha]_D^{25}$ +16.05 (*c* 1.19, $CHCl_3$) [Found $(M+Na)^+$: 349.2717; $C_{20}H_{38}O_3+Na$ requires: 349.2718]. This showed δ_H (500 MHz, $CDCl_3$): 4.03 (2H, t, *J* 6.6 Hz), 3.75–3.66 (2H, m), 1.70 (1H, sext., *J* 7.0 Hz), 1.66 (1H, br pent, *J* 6.7 Hz), 1.53 (1H, br sext., *J* 7.0 Hz), 1.40–1.17 (22H, m, including s at δ 1.20), 1.16–1.1 (1H, m), 0.94 (3H, d, *J* 6.7 Hz), 0.87–0.80 (1H, m), 0.50–0.44 (1H, m), 0.24–0.12 (3H, m); δ_C (126 MHz, $CDCl_3$): 178.7, 64.4, 61.2, 40.3, 38.7, 34.9, 34.3, 29.5, 29.45, 29.4, 29.1, 28.5, 27.2, 25.9, 25.8, 19.8, 18.6, 10.6; ν_{max}: 3363, 2925, 2854, 1731 cm^{-1}.

*3.1.3. (17S,18S)-17-(tert-Butyldimethylsilanyloxy)-18-methyl-hexatriacontan-1-ol (**12**).* 2,2-Dimethylpropionic acid (17S,18S)-17-(*tert*-butyldimethyl-silanyloxy)-18-methylhexatriacontyl ester (3.50 g, 4.66 mmol) (see Supplementary data) in dry THF (10 mL) was added dropwise over 15 min to a suspension of lithium aluminium hydride (0.265 g, 6.99 mmol) in THF (25 mL) at 0 °C under nitrogen. The mixture was allowed to reach room temperature, heated to reflux for 1 h, then quenched with satd aq sodium sulfate decahydrate at 0 °C until a white precipitate had formed. THF (50 mL) was added and the mixture was stirred at room temperature for 30 min, filtered through a bed of silica and the solvent evaporated. Column chromatography eluting with petrol/ethyl acetate (10:1) gave the title compound as a colourless oil, **12** (2.9 g, 93%), $[\alpha]_D^{24}$ −5.4 (*c* 1.01, $CHCl_3$) [Found $(M+Na)^+$: 689.6622, $C_{43}H_{90}O_2Si+Na$ requires: 689.6602]. This showed δ_H (500 MHz, $CDCl_3$): 3.65 (2H, t, *J* 6.6 Hz), 3.53–3.50 (1H, m), 1.61–1.55 (2H, m), 1.51–1.43 (2H, m), 1.40–1.26 (60H, m, v br), 1.10–1.02 (1H, m), 0.89 (12H, m, including an s), 0.81 (3H, d, *J* 6.6 Hz), 0.04 (3H, s), 0.03 (3H, s); δ_C (126 MHz, $CDCl_3$): 75.9, 63.1, 37.8, 33.6, 32.9, 32.6, 31.9, 30.0, 29.9, 29.7 (v br), 29.68, 29.65, 29.62, 29.6, 29.5, 29.4, 27.7, 26.0, 25.9, 25.8, 22.7, 18.2, 14.4, 14.1, −4.2, −4.4; ν_{max}/cm^{-1}: 3332, 2924, 2854, 1465, 1253, 1058.

*3.1.4. 5-[(17S,18S)-17-(tert-Butyldimethylsilanyloxy)-18-methyl-hexatriacontylsulfonyl]-1-phenyl-1H-tetrazole (**13**).*

(i) *N*-Bromosuccinimide (0.69 g, 3.90 mmol) was added in portions over 15 min to a stirred solution of alcohol **12** (2.00 g, 2.89 mmol) and triphenylphosphine (0.905 g, 3.45 mmol) in dichloromethane (30 mL) at 0 °C. The mixture was stirred at room temperature for 1 h then quenched with satd aq sodium *meta*-bisulfate (30 mL). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×30 mL). The combined organic layers were washed with water, dried and evaporated to give a residue. The residue was treated with a mixture of petrol/ether (1:1) (50 mL) and heated at reflux for 30 min, then the triphenylphosphine oxide was filtered off and washed with petrol/ether (50 mL) and the filtrate evaporated. Column chromatography eluting with 10:2 petrol/ether gave a colourless oil, [(1*S*,2*S*)-1-(16-bromohexadecyl)-2-methyleicosyl-oxy]-*tert*-butyldimethylsilane (2.0 g, 91%), $[\alpha]_D^{23}$ −5.2 (*c* 1.08, $CHCl_3$) [Found $(M+Na)^+$: 751.5762, $C_{43}H_{89}{}^{79}BrOSi+Na$ requires: 751.5763]. This showed δ_H (500 MHz, $CDCl_3$): 3.5 (1H, br, m), 3.42 (2H, t, *J* 7.0 Hz), 1.87 (2H, br pent, *J* 6.65 Hz), 1.56–1.20 (63H, m), 0.97–0.80 (12H, including s at δ 0.89), 0.82 (3H, d, *J* 6.9 Hz), 0.04 (3H, s), 0.03 (3H, s); δ_C (126 MHz, $CDCl_3$): 75.8, 37.7, 33.9, 33.5, 32.9, 32.5, 31.9, 30.0, 29.9, 29.73, 29.71, 29.7, 29.65, 29.6, 29.5, 29.4, 28.8, 28.2, 27.7, 26.0, 25.9, 22.7, 18.2, 14.4, 14.1, −4.2, −4.4; ν_{max}: 2929, 2849, 1099, 717 cm^{-1}.

(ii) The above bromide (1.96 g, 2.69 mmol) was added to a stirred solution of 1-phenyl-1*H*-tetrazol-5-thiol (0.530 g, 2.95 mmol) and potassium carbonate (0.74 g, 5.37 mmol) in acetone (40 mL) and THF (15 mL) at room temperature. The mixture was stirred for 18 h, then the solvent was evaporated and the residue diluted with a mixture of petrol/ether (1:1, 50 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with the same solvent mixture (2×30 mL). The combined organic layers were dried and evaporated. Column chromatography eluting with petrol/ether (5:1) gave a colourless viscous oil, 5-[(17*S*,18*S*)-17-(*tert*-butyldimethyl-silanyloxy)-18-methylhexatriacontyl-sulfanyl]-1-phenyl-1*H*-tetrazole (2.11 g, 95%), $[\alpha]_D^{22}$ −4.08 (*c* 1.25, $CHCl_3$) [Found $(M+Na)^+$: 849.6838, $C_{50}H_{94}N_4OSSi+Na$ requires: 849.6815]. This showed δ_H (500 MHz, $CDCl_3$): 7.57–7.52 (5H, m), 3.52–3.49 (1H, m), 3.4 (2H, t, *J* 7 Hz), 1.82 (2H, pent, *J* 7 Hz), 1.57–1.12 (62H, m), 1.09–1.0 (1H, m), 0.96–0.84 (12, including s at δ 0.89), 0.8 (3H, d, *J* 6.7 Hz), 0.034 (3H, s), 0.025 (3H, s); δ_C (126 MHz, $CDCl_3$): 154.4, 133.8, 129.9, 129.7, 123.7, 75.8, 37.7, 33.5, 33.3, 32.5, 31.9, 30.0, 29.8, 29.7, 29.5, 29.4, 29.3, 29.1, 29, 28.6, 27.7, 25.9, 25.88, 22.6, 18.1, 14.4, 14.1, −4.2, −4.5; ν_{max}: 2928, 2861, 1097 cm^{-1}.

(iii) Ammonium heptamolybdate(VI) tetrahydrate (1.5 g, 1.2 mmol) in ice cold aq hydrogen peroxide (35% w/w, 15 mL) was added dropwise to a stirred solution of the tetrazole (2.00 g, 2.42 mmol) in a mixture of methylated spirit (30 mL) and tetrahydrofuran (30 mL) at 5 °C. The resulting yellow solution was stirred for 1 h at room temperature, then further ice cold ammonium heptamolybdate(VI) tetrahydrate (1.5 g, 1.2 mmol)

in hydrogen peroxide (15 mL) was added. The mixture was stirred at room temperature for 16 h, then dichloromethane (60 mL) was added followed by water (200 mL). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×30 mL). The combined organic layers were washed with water, dried and evaporated to give a residue. Column chromatography eluting with petrol/ether (5:2) gave a white solid, the title compound **13** (1.7 g, 82%), $[\alpha]_D^{22}$ −3.74 (*c* 1.15, $CHCl_3$) [Found $(M+Na)^+$: 881.6722, $C_{50}H_{94}N_4O_3SSi+Na$ requires: 881.6713]. This showed δ_H (500 MHz, $CDCl_3$): 7.73–7.71 (2H, m), 7.65–7.61 (3H, m), 3.74 (2H, distorted t, *J* 7.85 Hz), 3.5 (1H, br, sextet, *J* 3.43 Hz), 1.96 (2H, br pent, *J* 7.6 Hz), 1.5 (2H, pent, *J* 7.55 Hz), 1.4–1.15 (60H, m), 1.06–1.01 (1H, m), 0.9–0.87 (12H, including s at δ 0.89), 0.8 (3H, d, *J* 6.65 Hz), 0.04 (3H, s), 0.03 (3H, s); δ_C (126 MHz, $CDCl_3$): 153.5, 133.1, 131.4, 129.7, 125.1, 75.9, 56, 37.7, 33.5, 32.5, 31.9, 30.0, 29.9, 29.7, 29.65, 29.6, 29.5, 29.4, 29.2, 28.9, 28.1, 27.7, 25.96, 25.9, 22.7, 21.9, 18.2, 14.4, 14.1, −4.2, −4.4; ν_{max}: 2924, 2849, 1343, 1157, 1096 cm^{-1}.

*3.1.5. 2,2-Dimethylpropionic acid 8-[(1S,2R)-2-((S)-1-methyl-3-oxopropyl)cyclopropyl]octyl ester (**14**).* A solution of alcohol **11** (*n*=7) (0.9 g, 2.8 mmol) in dichloromethane (10 mL) was added to a stirred suspension of PCC (1.78 g, 8.28 mmol) in dichloromethane (50 mL). The mixture was stirred for 2 h at room temperature then diluted with ether (250 mL), filtered through a bed of silica and the solvent was evaporated. Column chromatography eluting with petrol/ether (3:1) gave the title compound as a colourless oil, **14** (0.81 g, 91%), $[\alpha]_D^{25}$ +22.5 (*c* 1.42, $CHCl_3$) [Found $(M+Na)^+$: 347.2535, $C_{20}H_{36}O_3+Na$ requires: 347.2562]. This showed δ_H (500 MHz, $CDCl_3$): 9.8 (1H, t, *J* 2.5 Hz), 4.04 (2H, t, *J* 6.6 Hz), 2.52 (1H, ddd, *J* 2.5, 6.0, 15.8 Hz), 2.39 (1H, ddd, *J* 2.5, 7.6, 15.8 Hz), 1.61 (2H, pent, 6.6 Hz), 1.34–1.26 (12H, m), 1.19 (9H, s), 1.16–1.12 (1H, m), 1.02 (3H, d, *J* 6.6 Hz), 0.51–0.45 (1H, m), 0.34–0.18 (3H, m); δ_C (126 MHz, $CDCl_3$): 202.9, 178.6, 64.4, 51.4, 34.0, 33.9, 29.5 29.46, 29.4, 29.2, 28.6, 27.2, 25.9, 25.6, 19.9, 18.8, 11.4; ν_{max}: 2922, 2853, 1729 cm^{-1}.

*3.1.6. 8-{(1S,2R)-2-[(1S,20S,21S)-20-(tert-Butyldimethylsilanyloxy)-1,21-dimethylnonatriacontyl]-cyclopropyl}-octan-1-ol (**15**).*

(i) Aldehyde **14** (0.73 g, 2.25 mmol) was dissolved in dry THF (15 mL) and a solution of 5-[(17*S*,18*S*)-17-(*tert*-butyldimethylsilanyloxy)-18-methylhexatriacontylsulfonyl]-1-phenyl-1*H*-tetrazole **13** (1.93 g, 2.25 mmol) in dry THF (20 mL) was added at room temperature. This solution was cooled to −12 °C and lithium bis(trimethylsilyl)amide (3.57 mL, 3.37 mmol, 1.06 M) was added at between −12 and −4 °C. The solution was allowed to reach room temperature and stirred for 2 h. Petrol/ether (1:1, 100 mL) and satd aq ammonium chloride (30 mL) were added. The organic phase was separated and water layer was extracted with petrol/ether (1:1, 2×75 mL). The combined organic layers were dried and the solvent was evaporated. The product was purified by column chromatography eluting with petrol/ether (30:1) to give a colourless oil, (*E*/*Z*)-2,2-dimethylpropionic acid 8-{(1*S*,2*R*)-2-[(1*S*,20*S*,21*S*)-20-(*tert*-butyl-dimethylsilanyloxy)-1,21-dimethylnonatriacont-3-enyl]-cyclopropyl}octyl ester (1.5 g, 70%) as a mixture of two isomers in ratio 3:1. Dipotassium azodicarboxylate (3.9 g, 2.0 mmol) was added to a stirred solution of the above alkene (1.40 g, 1.46 mmol) in dry THF (15 mL) and methanol (3 mL) at 10 °C under nitrogen, resulting in a yellow suspension. Acetic acid (3 mL) in THF (3 mL) was added dropwise over 8 h, after which a white precipitate had formed. The mixture was stirred for 16 h then slowly poured into satd aq $NaHCO_3$ (50 mL). The product was extracted with petrol/ether (20:1) (30 mL) and the aqueous layer was re-extracted with petrol/ether (20:1) (2×30 mL). The combined organic layers were dried and evaporated. The procedure was repeated for another 16 h. Column chromatography eluting with petrol/ether (30:1) then gave a colourless oil, 2,2-dimethylpropionic acid 8-{(1*S*,2*R*)-2-[(1*S*,20*S*,21*S*)-20-(*tert*-butyldimethylsilanyloxy)-1,21-dimethylnonatriacontyl]cyclopropyl}octyl ester (1.05 g, 75%), $[\alpha]_D^{23}$ −1.3 (*c* 0.93, $CHCl_3$) [Found $(M+Na)^+$: 981.9379, $C_{63}H_{126}O_3Si+Na$ requires: 981.9373]. This showed δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.6 Hz), 3.52–3.49 (1H, m), 1.63 (2H, br pent, *J* 6.6 Hz), 1.55–1.16 (82H, br m and s at δ 1.21 for 9H), 1.08–1.01 (1H, m), 0.91–0.88 (15H, m, including s and t, *J* 6.6 Hz), 0.80 (3H, d, *J*7.0 Hz), 0.71–0.64 (1H, m), 0.48–0.42 (1H, m), 0.22–0.09 (3H, m), 0.04 (3H, s), 0.03 (3H, s); δ_C (126 MHz, $CDCl_3$): 178.6, 75.9, 64.5, 38.7, 38.1, 37.7, 37.4, 34.5, 33.5, 32.5, 31.9, 30.1, 30.0, 29.9, 29.72, 29.7 (v br), 29.66, 29.60, 29.56, 29.49, 29.4, 29.3, 28.6, 27.7, 27.3, 27.2, 26.1, 26.0, 25.9, 22.7, 19.7, 18.6, 18.2, 14.4, 14.1, 10.5, −4.2, −4.4; ν_{max}: 2924, 2853, 1733, 1464, 1284, 1253, 1154, 1075 cm^{-1}.

(ii) The above ester (0.80 g, 0.83 mmol) in dry THF (5 mL) was added dropwise over 15 min to a suspension of lithium aluminium hydride (0.063 g, 1.67 mmol) in THF (5 mL) at 0 °C under nitrogen. The mixture was allowed to reach room temperature, heated at reflux for 1 h, then satd aq sodium sulfate decahydrate was added at 0 °C until a white precipitate had formed. THF (20 mL) was added and the mixture was stirred at room temperature for 30 min, filtered through a bed of silica and the solvent evaporated. Column chromatography eluting with 5:2 petrol/ether gave the title compound as a colourless oil, **15** (0.6 g, 82%), $[\alpha]_D^{25}$ −0.64 (*c* 1.4, $CHCl_3$) [Found $(M+Na)^+$: 897.8788, $C_{58}H_{118}O_2Si+Na$ requires: 897.8798]. This showed δ_H (500 MHz, $CDCl_3$): 3.65 (2H, t, *J* 6.6 Hz), 3.52–3.49 (1H, m), 1.60–1.54 (2H, m), 1.48–1.16 (82H, m, v br), 1.08–1.01 (1H, m), 0.93–0.88 (15H, m, including s for the *tert*-butyl), 0.80 (3H, d, *J* 6.6 Hz), 0.71–0.64 (1H, m), 0.48–0.43 (1H, m), 0.21–0.09 (3H, m), 0.04 (3H, s), 0.03 (3H, s); δ_C (126 MHz, $CDCl_3$): 75.9, 63.1, 38.1, 37.7, 37.4, 34.5, 33.6, 32.8, 32.5, 31.9, 30.1, 30.0, 29.9, 29.74, 29.72, 29.69, 29.67, 29.66, 29.64, 29.5, 29.4, 27.7, 27.3, 26.1, 26.0, 25.9, 25.8, 22.7, 19.7, 18.6, 18.2, 14.4, 14.1, 10.5, −4.2, −4.4; ν_{max}: 3332, 2924, 2853, 1464, 1253, 1058 cm^{-1}.

*3.1.7. 8-{(1S,2R)-2-[(1S,20S,21S)-20-(tert-Butyldimethylsilanyloxy)-1,21-dimethylnonatriacontyl]-cyclopropyl}octanal (**16**).* A solution of alcohol **15** (0.43 g, 0.49 mmol) in dichloromethane (10 mL) was added to a stirred suspension of PCC (0.32 g, 1.47 mmol) in dichloromethane (10 mL). After 2 h at room temperature, it was diluted with ether (20 mL), filtered through a bed of silica and the solvent was evaporated. Column chromatography eluting with petrol/ether (10:1) gave the title compound as a colourless oil, **16** (0.37 g, 86%), $[\alpha]_D^{25}$ −0.71 (*c* 0.52, $CHCl_3$) [Found $(M+Na)^+$: 895.8627, $C_{58}H_{116}O_2Si+Na$ requires: 895.8637]. This showed δ_H (500 MHz, $CDCl_3$): 9.77 (1H, t, *J* 1.9 Hz), 3.52–3.49 (1H, m), 2.43 (2H, dt, *J* 1.9, 7.3 Hz), 1.64 (2H, br pent, *J* 7.3 Hz), 1.58–1.01 (81H, m, v br), 0.91–0.88 (15H, m, including s and t, *J* 7.3 Hz), 0.80 (3H, d, *J* 7.0 Hz), 0.70–0.65 (1H, m), 0.47–0.43 (1H, m), 0.22–0.09 (3H, m), 0.04 (3H, s), 0.03 (3H, s); δ_C (126 MHz, $CDCl_3$): 202.9, 75.9, 43.9, 38.1, 37.7, 37.4, 34.4, 33.5, 32.5, 31.9, 30.1, 30.0, 29.9, 29.72, 29.70 (v br), 29.65, 29.60, 29.5, 29.4, 29.35, 29.3, 29.2, 27.7, 27.3, 26.1, 26.0, 25.9, 22.7, 22.1, 19.7, 18.6, 18.2, 14.4, 14.1, 10.5, −4.2, −4.4; ν_{max}: 2925, 2854, 1731, 1465, 1375, 1253, 1076 cm^{-1}.

*3.1.8. (R)-2-[(R)-9-Bromo-1-(tert-butyldimethylsilanyloxy)non-3-enyl]hexacosanoic acid methyl ester (**19**).* Lithium bis(trimethylsilyl) amide (9.38 mL, 9.95 mmol, 1.06 M) was added to a stirred solution of (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-3-oxopropyl]hexacosanoic acid methyl ester (**18**)[37] (2.90 g, 4.87 mmol) and 5-(6-

bromohexane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**17**)[31] (2.85 g, 7.65 mmol) in dry THF (100 mL) at −12 °C under nitrogen. The reaction was stirred at room temperature for 3 h then quenched by addition of satd aq ammonium chloride (100 mL), extracted with petrol/ether (1:1, 3×150 mL), dried and the solvent was evaporated. Column chromatography eluting with petrol/ether (20:1) gave a colourless oil, (*R*)-2-[(*E*/*Z*)-(*R*)-9-bromo-1-(*tert*-butyldimethylsilanyloxy)-non-3-enyl]hexacosanoic acid methyl ester (3.41 g, 94%), as a mixture of two isomers in ratio 2:1. Palladium (10% on carbon, 0.6 g) was added to a stirred solution of the above alkene (3.41 g, 4.58 mmol) in THF (40 mL) and ethanol (40 mL). Hydrogenation was carried out for 16 h. The solution was filtered over a bed of Celite and the solvent was evaporated. Column chromatography eluting with petrol/ether (20:1) gave the title compound **19** as a colourless oil (1.23 g, 36%), $[\alpha]_D^{26}$ −2.1 (*c* 1.35, $CHCl_3$) [Found $(M+Na)^+$: 767.5372 $C_{42}H_{85}{}^{79}BrO_3Si$ + Na requires: 767.5344]. This showed δ_H (500 MHz, $CDCl_3$): 3.93–3.89 (1H, m), 3.66 (3H, s), 3.41 (2H, t, *J* 7.0 Hz), 2.53 (1H, ddd, *J* 3.8, 7.3, 10.7 Hz), 1.86 (2H, quintet, *J* 7.0 Hz), 1.60–1.54 (5H, m including s at δ 1.55), 1.52–1.38 (6H, m), 1.33–1.12 (47H, m), 0.91–0.83 (12H, including t at δ 0.89, *J* 6.9 Hz and s at δ 0.87), 0.00 (3H, s), −0.02 (3H, s), δ_C (126 MHz, $CDCl_3$): 175.0, 73.15, 51.58, 51.19, 34.7, 33.9, 33.6, 32.8, 31.9, 29.7 (v br), 29.65, 29.6, 29.4, 28.7, 28.1, 27.8, 27.5, 25.7, 23.7, 22.7, 18.0, 14.1, −4.4, −4.9; ν_{max}: 2925, 2854, 1741, 1464, 1436, 1361, 1254, 1195, 1167, 1062, 1006, 939, 836, 813, 776, 722, 665 cm^{-1}.

*3.1.9. (R)-2-[(R)-1-Acetoxy-9-(5-phenyl-5H-tetrazol-1-sulfonyl)-nonyl]hexacosanoic acid methyl ester (**20**).*

(i) 1-Phenyl-1*H*-tetrazole-5-thiol (0.30 g, 1.69 mmol), methyl ester **19** (1.20 g, 1.61 mmol), anhydrous potassium carbonate (0.47 g, 3.38 mmol) and acetone (50 mL) were vigorously stirred for 18 h at room temperature. Water (100 mL) was added and the mixture was extracted with dichloromethane (150 mL, 2×100 mL). The combined organic phases were washed with brine (2×100 mL), dried and the solvent was evaporated. Column chromatography eluting with 4:1 petrol/ether gave a colourless oil, (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-9-(5-phenyl-5*H*-tetrazol-1-ylsulfanyl)-nonyl]hexacosanoic acid methyl ester (1.08 g, 79%), $[\alpha]_D^{26}$ −3.5 (*c* 0.65, $CHCl_3$) [Found $(M+Na)^+$: 865.6393, $C_{49}H_{90}N_4O_3SSi$+Na requires: 865.6395]. This showed δ_H (500 MHz, $CDCl_3$): 7.61–7.52 (5H, m), 3.89–3.86 (1H, m), 3.63 (3H, s), 3.38 (2H, t, *J* 7.3 Hz), 2.50 (1H, ddd, *J* 3.8, 7.3, 10.7 Hz), 1.80 (2H, quintet, *J* 7.6 Hz), 1.62–1.58 (1H, v br s), 1.55–1.34 (6H, m), 1.33–1.07 (51H, br m), 0.96–0.79 (12H, m including t at δ 0.86, *J* 6.3 Hz and s at δ 0.84), 0.02 (3H, s), 0.00 (3H, s); δ_C (126 MHz, $CDCl_3$): 175.0, 154.5, 133.8, 130.0, 129.7, 123.8, 73.2, 51.6, 51.2, 33.6, 33.4, 31.9, 29.7, 29.6, 29.58, 29.4, 29.38, 29.3, 29.1, 29.0, 28.6, 27.7, 27.4, 25.7, 22.7, 22.6, 18.0, 14.1, −4.4, −4.9; ν_{max}: 2929, 2854, 1739, 1501, 1464, 1278, 1195, 1073, 836, 760, 694 cm^{-1}.

(ii) The above methyl ester (1.08 g, 1.28 mmol) was stirred in dry THF (20 mL) in a dry polyethylene vial under argon at room temperature. Pyridine (0.4 mL, 1.3 mmol) and HF·Pyridine (1.5 mL) was 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 with satd aq $NaHCO_3$ until no more carbon dioxide was liberated. The mixture was separated and the aqueous layer was re-extracted with petrol/ether (1:1, 2×100 mL). The combined organic layers were washed with brine and dried and the solvent was evaporated. Column chromatography eluting with petrol/ether (5:2) gave a white solid, (*R*)-2-[(*R*)-1-hydroxy-9-(5-phenyl-5*H*-tetrazol-1-ylsulfanyl)nonyl]hexacosanoic acid methyl ester (0.93 g, 81%), $[\alpha]_D^{17}$ +7.7 (*c* 0.50, $CHCl_3$), mp 76–78 °C [Found $(M+Na)^+$: 751.5530, $C_{43}H_{76}N_4O_3S$+Na requires: 751.5530]. This showed δ_H (500 MHz, $CDCl_3$): 7.61–7.52 (5H, m), 3.72 (3H, s), 3.65 (1H, br pent, *J* 3.8 Hz), 3.40 (2H, t, *J* 7.6 Hz), 2.44 (1H, dt, *J* 5.4, 9.1 Hz), 1.97–1.88 (2H, v br m), 1.82 (2H, quintet, *J* 7.6 Hz), 1.75–1.67 (1H, m), 1.63–1.56 (1H, m), 1.46–1.39 (5H, m), 1.38–1.10 (50H, br m), 0.89 (3H, t, *J* 7.0 Hz); δ_C (126 MHz, $CDCl_3$): 176.2, 154.5, 133.8, 130.0, 129.7, 123.8, 72.2, 51.4, 50.0, 35.6, 33.3, 31.9, 29.7, 29.6, 29.5, 29.48, 29.40, 29.37, 29.3, 29.31, 29.0, 28.9, 28.6, 27.4, 25.7, 22.7, 14.1; ν_{max}: 3494, 2921, 1720, 1596, 1500, 1464, 1378, 1300, 1278, 1239, 1190, 1131, 1077 cm^{-1}.

(iii) A mixture of acetic anhydride (11 mL) and anhydrous pyridine (11 mL) was added to stirred solution of the above ester (0.75 g, 1.03 mmol) in dry toluene (30 mL) at room temperature and the mixture was stirred for 18 h, diluted with toluene (20 mL) and the solvent was evaporated under reduced pressure to give a solid. This was purified by column chromatography eluting with petrol/ether (5:1) to give a white solid, (*R*)-2-[(*R*)-1-acetoxy-9-(5-phenyl-5*H*-tetrazol-1-ylsulfanyl)nonyl] hexacosanoic acid methyl ester (0.66 g, 84%), $[\alpha]_D^{17}$ +7.2 (*c* 0.47, $CHCl_3$), mp 42–44 °C [Found $(M+Na)^+$: 793.5647, $C_{45}H_{78}N_4O_4S$+Na requires: 793.5636]. This showed δ_H (500 MHz, $CDCl_3$): 7.60–7.52 (5H, m), 5.08 (1H, ddd, *J* 3.8, 7.0, 10.8 Hz), 3.67 (3H, s), 3.39 (2H, t, *J* 7.3 Hz), 2.61 (1H, ddd, *J* 4.1, 6.6, 10.7 Hz), 2.02 (3H, s), 1.81 (2H, quintet, *J* 7.6 Hz), 1.67–1.48 (4H, br m), 1.43 (3H, br pent, *J* 7.3 Hz), 1.35–1.10 (51H, br m), 0.88 (3H, t, *J* 7.0 Hz); δ_C (126 MHz, $CDCl_3$): 173.6, 170.3, 154.4, 133.8, 130.0, 129.7, 123.8, 74.0, 51.5, 49.6, 41.3, 34.1, 33.3, 31.9, 31.7, 29.7 (v br), 29.5, 29.4, 29.4, 29.31, 29.3, 29.2, 29.0, 28.9, 28.5, 28.1, 27.4, 24.9, 22.6, 22.3, 21.0, 14.1; ν_{max}: 2918, 2850, 1743, 1597, 1500, 1468, 1435, 1385, 1239, 1166, 1074, 1018 cm^{-1}.

(iv) *m*-Chloroperbenzoic acid (0.54 g, 1.56 mmol) in dichloromethane (20 mL) was added at 0 °C to a solution of the above ester (0.60 g, 0.78 mmol) and $NaHCO_3$ (0.29 g, 3.51 mmol) in dichloromethane (15 mL) and stirred at room temperature for 20 h. The mixture was quenched by addition of satd aq $NaHCO_3$ (20 mL) and extracted with dichloromethane (80 mL, 3×30 mL). The combined organic phases were washed with water (80 mL), dried and evaporated. Column chromatography eluting with petrol/ether (5:1) gave the title compound as a white solid **20** (0.55 g, 88%), $[\alpha]_D^{23}$ +9.0 (*c* 0.78, $CHCl_3$) [Found $(M+Na)^+$: 825.5552, $C_{45}H_{78}N_4O_6S$+Na requires: 825.5534]. This showed δ_H (500 MHz, $CDCl_3$): 7.72–7.68 (2H, m), 7.66–7.58 (3H, m), 5.09 (1H, ddd, *J* 4.1, 7.3, 10.7 Hz), 3.73 (2H, distorted t, *J* 7.0 Hz), 2.61 (1H, ddd, *J* 4.1, 6.6, 10.7 Hz), 2.04 (3H, s), 1.95 (2H, br quintet, *J* 7.9 Hz), 1.68–1.57 (3H, m), 1.56–1.41 (4H, m), 1.39–1.08 (54H, br m), 0.89 (3H, t, *J* 7.0 Hz); δ_C (126 MHz, $CDCl_3$): 173.6, 170.4, 153.5, 133.0, 131.4, 129.7, 125.1, 74.0, 56.0, 51.5, 49.6, 31.9, 13.7, 29.7 (v br), 29.6, 29.54, 29.5, 29.4, 29.3, 29.2, 29.0, 28.8, 28.11, 28.05, 27.5, 25.0, 22.7, 21.9, 21.0, 14.1; ν_{max}: 3449, 2923, 1732, 1594, 1499, 1463, 1377, 1341, 1244, 1152, 1017, 961 cm^{-1}.

*3.1.10. (R)-2-((R)-1-Acetoxy-17-{(1S,2R)-2-[(1S,20S,21S)-20-(tert-butyldimethylsilanyloxy)-1,21-dimethyl-nonatriacontyl]cyclopropyl} heptadecyl)hexacosnoic acid methyl ester (**21**).* Ester **20** (0.40 g, 0.50 mmol) was dissolved in dry THF (10 mL) and a solution of 8-{(1*S*,2*R*)-2-[(1*S*,20*S*,21*S*)-20-(*tert*-butyl-dimethylsilanyloxy)-1,21-dimethyl-nonatriacontyl]cyclopropyl}-octanal (**16**) (0.30 g, 0.34 mmol) in dry THF (10 mL) was added at room temperature. This solution was cooled to −12 °C and lithium bis(trimethylsilyl)amide (0.80 mL, 0.85 mmol, 1.06 M) was added. The solution was allowed to reach room temperature and stirred for 2 h. Ether (25 mL) and satd aq ammonium chloride (30 mL) were added. The organic phase was separated and the aq layer was extracted with petrol/ether (20:1, 2×40 mL). The combined organic layers were dried and

the solvent was evaporated. Column chromatography eluting with petrol/ether (20:1) gave a colourless oil, (*R*)-2-((*E*/*Z*)-(*R*)-1-acetoxy-17-{(1*S*,2*R*)-2-[(1*S*,20*S*,21*S*)-20-(*tert*-butyldimethyl-silanyloxy)-1,21-dimethylnonatriacontyl]cyclopropyl}heptadec-9-enyl)hexacosnoic acid methyl ester (0.23 g, 47%) as a mixture of two isomers in ratio 2.6:1. Dipotassium azodicarboxylate (2.0 g, 10.3 mmol) was added to a stirred solution of the alkenes (200 mg, 0.14 mmol) in THF (10 mL) and methanol (2 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 room temperature for 2 h. The other half of the glacial acetic acid solution was then added and the mixture was stirred overnight. Further dipotassium azodicarboxylate (2.0 g) and glacial acetic acid (2 mL) were added and stirred 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 the solvent was evaporated. The procedure was repeated. Column chromatography eluting with petrol/ether (20:1) gave the title compound as a white solid, **21** (150 mg, 75%), $[\alpha]_D^{13}$ +2.08 (*c* 0.64, $CHCl_3$) [Found $(M+Na)^+$: 1474.4282, $C_{96}H_{190}O_5Si+Na$ requires: 1474.4280]. This showed δ_H (500 MHz, $CDCl_3$): 5.10 (1H, ddd, *J* 4.2, 6.9, 8.1 Hz), 3.69 (3H, s), 3.52–3.49 (1H, m), 2.62 (1H, ddd, *J* 4.2, 7.0, 10.7 Hz), 2.04 (3H, s), 1.68–1.16 (148H, m, v br), 1.09–1.02 (1H, m), 0.91–0.88 (18H, m, including s), 0.80 (3H, d, *J* 6.6 Hz), 0.70–0.65 (1H, m), 0.49–0.43 (1H, m), 0.23–0.09 (3H, m), 0.04 (3H, s), 0.03 (3H, s); δ_C (126 MHz, $CDCl_3$): 173.6, 170.3, 75.9, 74.1, 51.5, 49.6, 38.1, 37.8, 37.4, 34.5, 33.6, 32.5, 31.9, 31.7, 30.1, 30.0, 29.9, 29.74, 29.72 (v br), 29.67, 29.64, 29.59, 29.57, 29.49, 29.47, 29.45, 29.41, 29.37, 28.1, 27.7, 27.5, 27.3, 26.2, 26.0, 25.9, 25.0, 22.7, 21.0, 19.7, 18.6, 18.2, 14.4, 14.1, 10.5, −4.2, −4.4; ν_{max}: 2925, 2853, 1746, 1465, 1372, 1248, 1023 cm^{-1}.

*3.1.11. (R)-2-((R)-1-Acetoxy-17-{(1S,2R)-2-[(1S,20S,21S)-20-hydroxy-1,21-dimethylnonatriacontyl]-cyclopropyl}-heptadecyl)-hexacosnoic acid methyl ester (**22**).* The ester **21** (0.140 g, 0.096 mmol) was stirred in dry THF (9.0 mL) in a dry polyethylene vial under argon at room temperature. Pyridine (0.2 mL) and HF·pyridine (1.3 mL) were added and the mixture was stirred for 17 h at 45 °C, then diluted with petrol/ether (1:1, 10 mL) and neutralized with 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, 2×50 mL). The combined organic layers were washed with brine and dried, and the solvent was evaporated. Column chromatography eluting with petrol/ether (5:1) gave the title compound as a white solid **22** (95 mg, 74%), $[\alpha]_D^{21}$ −0.81 (*c* 0.74, $CHCl_3$), mp 43–44 °C [Found $(M+Na)^+$: 1360.3449, $C_{90}H_{176}O_5+Na$ requires: 1360.3415]. This showed δ_H (500 MHz, $CDCl_3$): 5.09 (1H, ddd, *J* 4.4, 6.9, 8.2 Hz), 3.68 (3H, s), 3.52–3.49 (1H, m), 2.62 (1H, ddd, *J* 4.4, 6.9, 10.7 Hz), 2.04 (3H, s), 1.67–1.14 (150H, m, v br), 0.90 (3H, d, *J* 6.6 Hz), 0.89 (3H, t, *J* 6.9 Hz), 0.86 (3H, d, *J* 6.9 Hz), 0.71–0.64 (1H, m), 0.48–0.42 (1H, m), 0.22–0.09 (3H, m); δ_C (126 MHz, $CDCl_3$): 173.6, 170.3, 75.2, 74.1, 51.5, 49.6, 38.2, 38.1, 37.4, 34.51, 34.49, 33.4, 31.9, 31.7, 30.1, 30.0, 29.72, 29.7 (v br), 29.65, 29.6, 29 5, 29 4, 29.39, 29.36, 28.1, 27.5, 27.4, 27.3, 26.3, 16.1, 25.0, 22.7, 21.0, 19.7, 18.6, 14.1, 13.6, 10.5; ν_{max}: 3489, 2850, 1739, 1470, 1375, 1240, 1176, 1021 cm^{-1}.

*3.1.12. (R)-2-{(R)-1-Hydroxy-17-[(1S,2R)-2-((1S,20S,21S)-20-hydroxy-1,21-dimethylnonatriacontyl)-cyclopropyl]-heptadecyl}-hexacosanoic acid (**23**).* Lithium hydroxide monohydrate (28.2 mg, 0.67 mmol) was added to a stirred solution of ester **22** (0.030 g, 0.024 mmol) in THF (3 mL), methanol (0.2 mL) and water (0.2 mL) at room temperature. The mixture was stirred at 45 °C for 18 h, then cooled to room temperature, petrol/ethyl acetate (5:2, 10 mL) added and the mixture was acidified to pH 1 with 5% aq HCl by dropwise. Further petrol/ether (5:2, 20 mL) was added and extracted. The aqueous layer was re-extracted with petrol/ether (5:2, 4×20 mL). The combined organic layers were washed with water (10 mL), dried and the solvent evaporated. Column chromatography eluting with 3:1 petrol/ethyl acetate gave the title compound as a white solid, **23** (18 mg, 58%), $[\alpha]_D^{16}$ −1.04 (*c* 0.54, $CHCl_3$), mp 51–53 °C [Found $(M+Na)^+$: 1304.3184, $C_{87}H_{172}O_4+Na$ requires: 1304.3153]. This showed δ_H (500 MHz, $CDCl_3$): 3.73–3.69 (1H, m), 3.53–3.50 (1H, m), 2.46 (1H, dt, *J* 8.8, 5.4 Hz), 1.75–1.59 (1H, m), 1.55–1.12 (148H, m, v br), 0.91–0.86 (12H, m), 0.69–0.63 (1H, m), 0.48–0.42 (1H, m), 0.22–0.08 (3H, m); δ_C (126 MHz, $CDCl_3$): 178.8, 75.4, 72.1, 50.7, 38.2, 38.1, 37.4, 35.6, 34.5, 34.4, 33.3, 31.9, 30.1, 30.0, 29.73, 29.71 (v br), 29.66, 29.60, 29.54, 29.43, 29.36, 27.4, 27.3, 27.2, 26.3, 26.1, 25.7, 22.7, 19.7, 18.6, 14.1, 13.6, 10.5; ν_{max}: 3331, 2920, 2851, 1686, 1460, 1377, 1201 cm^{-1}.

*3.1.13. (R)-2-{(R)-17-[(1S,2R)-2-((1S,21S)-1,21-Dimethyl-20-oxononatriacontyl)-cyclopropyl]-1-hydroxyheptadecyl}-hexacosanoic acid methyl ester (**24**).* The ester **22** (60 mg, 0.045 mmol) was dissolved in dichloromethane (3 mL) and added in portions to a stirred solution of PCC (29 mg, 0.134 mmol) in dichloromethane (10 mL) at room temperature. The mixture was stirred for 3 h then diluted with ether (20 mL) and filtered through a bed of silica, and the solvent was evaporated. Column chromatography eluting with 5:1 petrol/ether gave the title compound as a white solid **24** (50 mg, 83%), $[\alpha]_D^{21}$ +9.12 (*c* 0.83, $CHCl_3$), mp 32–33 °C [Found $(M+Na)^+$: 1358.3206, $C_{90}H_{174}O_5+Na$ requires: 1358.3253]. This showed δ_H (500 MHz, $CDCl_3$): 5.10 (1H, br dt, *J* 4.0, 8.1 Hz), 3.69 (3H, s), 2.62 (1H, ddd, *J* 4.4, 7.0, 10.7 Hz), 2.51 (1H, sext, *J* 6.7 Hz), 2.43 (1H, dt, *J* 14.6, 7.6 Hz), 2.40 (1H, dt, *J* 14.6, 7.6 Hz), 2.03 (3H, s), 1.65–1.17 (146H, m, v br), 1.05 (3H, d, *J* 7.0 Hz), 0.90 (3H, d, *J* 7.0 Hz), 0.89 (6H, t, *J* 6.8 Hz), 0.70–0.65 (1H, m), 0.48–0.42 (1H, m), 0.22–0.09 (3H, m); δ_C (126 MHz, $CDCl_3$): 215.1, 173.6, 170.3, 74.1, 51.5, 49.6, 46.3, 41.1, 38.1, 37.4, 34.5, 33.0, 31.9, 31.7, 30.1, 29.72, 29.70 (v br), 29.67, 29.65, 29.60, 29.57, 29.55, 29.51, 29.48, 29.46, 29.44, 29.39, 29.35, 28.1, 27.5, 27.4, 27.3, 26.1, 25.0, 23.7, 22.7, 21.0, 19.7, 18.6, 16.4, 14.1, 10.5; ν_{max}: 2919, 2850, 1737, 1703, 1471, 1375, 1241, 1162 cm^{-1}.

*3.1.14. (R)-2-{(R)-17-[(1S,2R)-2-((1S,21RS)-1,21-Dimethyl-20-oxo-nonatriacontyl)-cyclopropyl]-1-hydroxy-heptadecyl}-hexacosanoic acid (**25**).* Lithium hydroxide monohydrate (45.2 mg, 1.08 mmol) was added to a stirred solution of the ester **24** (48 mg, 0.036 mmol) in THF (5 mL), methanol (0.2 mL) and water (0.2 mL) at room temperature. The mixture was stirred at 45 °C for 18 h, cooled to room temperature and diluted with petrol/ethyl acetate (5:2, 10 mL) then acidified to pH 1 by dropwise addition of 5% aq HCl. Further petrol/ethyl acetate (5:2, 30 mL) was added and extracted. The aqueous layer was re-extracted with petrol/ethyl acetate (5:2, 4×30 mL). The combined organic layers were washed with water (20 mL), dried and the solvent was evaporated. The product was purified by column chromatography eluting with petrol/ethyl acetate (7:2) to give the title compound as a white solid, **25** (37 mg, 79%), $[\alpha]_D^{19}$ +4.74 (*c* 0.78, $CHCl_3$), mp 66–68 °C [Found $(M+Na)^+$: 1302.2935, $C_{87}H_{170}O_4+Na$ requires: 1302.2991]. This showed δ_H (500 MHz, $CDCl_3$): 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), 1.78–1.14 (146H, m, v br), 1.05 (3H, d, *J* 6.9 Hz), 0.90 (3H, d, *J* 6.9 Hz), 0.89 (6H, t, *J* 6.9 Hz), 0.71–0.64 (1H, m), 0.48–0.42 (1H, m), 0.22–0.08 (3H, m); δ_C (126 MHz, $CDCl_3$): 215.4, 180.0, 72.1, 50.9, 46.3, 41.1, 38.1, 37.4, 35.5, 34.5, 33.0, 31.9, 30.1, 29.7 (v br), 29.66, 29.61, 29.52, 29.50, 29.47, 29.44, 29.37, 29.34, 27.3, 27.2, 26.1, 25.7, 23.7, 22.7, 19.7, 18.6, 16.3, 14.1, 10.5; ν_{max}: 3348, 2919, 2850, 1697, 1471, 1376, 1185, 1023 cm^{-1}.

*3.1.15. (R)-2-((R)-1-Acetoxy-17-{(1S,2R)-2-[(1S,20S,21S)-20-(tetrahydro-2H-pyran-2-yl)-1,21-dimethyl-nonatriacontyl]cyclopropyl} heptadecyl)hexacosnoic acid methyl ester (**30**).* Pyridinium *p*-toluene sulfonate (0.10 g, 0.36 mmol) in dry dichloromethane (1 mL) was added to a stirred solution of ester **22** (1.04 g, 0.720 mmol) and

freshly distilled dihydro-2H-pyran (0.12 mL, 1.4 mmol) in dry dichloromethane (5 mL) at room temperature under nitrogen. After stirring for 1.5 h, the reaction was quenched with satd aq $NaHCO_3$ (10 mL). The product was extracted with dichloromethane (3×50 mL) and the combined organic layers were dried and evaporated. Column chromatography, eluting with petrol/ethyl acetate (10:1) with a few drops of Et_3N gave the title compound as a white semi-solid as a mixture of diastereoisomers (1.04 g, 94%) [Found $(M+Na)^+$: 1444.3946. $C_{95}H_{184}O_6$+Na requires: 1444.4093], which showed δ_H (500 MHz, $CDCl_3$): 5.09 (1H, ddd, *J* 11.05, 8.2, 4.1 Hz), 4.65 (2H, td, *J* 16.4, 3.45 Hz), 3.90 (1H, m), 3.68 (3H, s), 3.49–3.43 (2H, m), 2.62 (1H, ddd, *J* 10.7, 6.95, 4.4 Hz), 2.03 (3H, s), 1.26 (148H, v br s), 0.90 (3H, d, *J* 6.6 Hz), 0.89 (6H, t, *J* 6.95 Hz), 0.87 (6H, t, *J* 4.7 Hz), 0.85 (3H, d, *J* 6.3 Hz), 0.7–0.64 (1H, m), 0.47–0.43 (1H, m), 0.22–0.09 (3H, m); δ_C (126 MHz, $CDCl_3$): 173.9, 98.5, 97.8, 81.5, 80.9, 74.1, 51.5, 49.6, 38.1, 37.4, 36.5, 35.2, 34.5, 32.5, 32.1, 31.9, 31.8, 31.5, 31.3, 31.2, 30.1, 30.0, 29.96, 29.7, 29.7, 29.7, 29.6, 28.5, 29.4, 29.35, 28.1, 27.6, 27.55, 27.5, 27.3, 26.2, 25.8, 25.7, 25.6, 25.0, 22.7, 21.0, 20.1, 19.8, 19.7, 18.6, 15.2, 14.9, 14.1, 10.5; ν_{max}/cm^{-1}: 2918, 2850, 1744, 1476, 1372, 1236, 1165, 1132, 1077, 1023, 721.

*3.1.16. (2R)-2-((1R)-1-(tert-Butyldimethylsilyloxy)-17-(2-((2S,21S, 22S)-22-methyl-21-(tetra-hydro-2H-pyran-2-yloxy)tetra-contan-2-yl)cyclopropyl)heptadecyl)hexacosanoic acid (**31**).*

(i) Lithium hydroxide monohydrate (0.46 g, 1.1 mmol) was added to a stirred solution ester **30** (1.04 g, 0.738 mmol) in THF (10 mL), methanol (1 mL) and water (1.2 mL) at room temperature. The mixture was stirred at 45 °C for 18 h. It was cooled to room temperature and a mixture of petrol/ethyl acetate (10:1, 10 mL) was added and then it was neutralized with aq HCl (5%) to pH 7. The mixture was extracted with petrol/ethyl acetate (5:2) (3×25 mL). The combined organic layers were washed with water (15 mL), dried and the solvent was evaporated. Column chromatography eluting with petrol/ethyl acetate (5:2) gave a semi-solid, (*R*)-2-{(*R*)-1-hydroxy-17-[(1*S*,2*R*)-2-((1*S*,20*S*,21*S*)-20-(tetrahydro-2*H*-pyran-2-yl)-1,21-dimethylnonatriacontyl) cyclopropyl]heptadecyl}hexacosanoic acid (1.00 g, 90%) [Found $(M+Na)^+$: 1388.3735 $C_{92}H_{180}O_5$+Na requires: 1388.3728], which showed δ_H (500 MHz, $CDCl_3$): 4.64 (1H, td, *J* 6.95, 3.45 Hz), 3.96–3.90 (1H, m), 3.73–3.71 (1H, m), 3.50–3.43 (2H, m), 2.46 (1H, dt, *J* 10.1, 5.35 Hz), 1.85–1.80 (1H, m), 1.76–1.62 (3H, m), 1.53–1.51 (4H, m), 1.26 (152H, v br s), 0.89 (6H, t, *J* 9.75 Hz), 0.85 (3H, d, *J* 6.95 Hz), 0.71–0.64 (1H, m), 0.48–0.42 (1H, m), 0.22–0.09 (3H, m); δ_C (126 MHz, $CDCl_3$): 173.1, 98.5, 97.8, 81.5, 80.9, 74.1, 51.5, 49.6, 38.1, 37.4, 36.5, 35.2, 34.5, 32.5, 32.1, 31.9, 31.8, 31.5, 31.3, 31.2, 30.1, 30.0, 29.96, 29.72, 29.7, 29.66, 29.6, 28.5, 29.4, 29.35, 28.1, 27.6, 27.55, 27.5, 27.3, 26.2, 25.8, 25.7, 25.6, 25.0, 22.7, 20.1, 19.8, 19.7, 18.6, 15.2, 14.9, 14.1, 10.5; ν_{max}/cm^{-1}: 3519, 2917, 2850, 1682, 1469, 1377, 1259, 1214, 1131, 1077, 1024, 868, 719.

(ii) Imidazole (0.50 g, 0.73 mmol) was added to a stirred solution of the above acid (0.95 g, 0.73 mmol) in dry DMF (5 mL) and dry toluene (10 mL) at room temperature followed by the addition of *tert*-butyldimethylsilylchloride (1.11 g, 0.730 mmol) and 4-dimethylaminopyridine (40 mg, 0.32 mmol). The mixture was stirred at 70 °C for 18 h, then the solvent was removed under high vacuum and the residue was diluted with petrol/ethyl acetate (1:1, 150 mL) and satd aq $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was re-extracted with petrol/ethyl acetate (3×50 mL). The combined organic layers were washed with water, dried and evaporated to give a residue. This was dissolved in THF (20 mL), water (2 mL), and methanol (1.5 mL), and potassium carbonate (0.5 g) was added. The mixture was stirred at 45 °C for 6 h, then diluted with petrol/ethyl acetate (10:1, 50 mL) and water (5 mL) then acidified with potassium hydrogen sulfate to a pH 2. The organic layer was separated and the aqueous layer was re-extracted with petrol/ethyl acetate (2×50 mL). The combined organic layers were washed with water, dried and evaporated. Column chromatography on silica eluting with petrol/ethyl acetate (20:1) to give a white semi-solid, the title compound **31** (0.92 g, 84%) [Found $(M+Na)^+$: 1502.4569. $C_{98}H_{194}O_5Si$+Na requires: 1502.4593]. This showed δ_H (500 MHz, $CDCl_3$): 4.66 (1H, dt, *J* 6.95, 3.5 Hz), 3.95–3.89 (1H, m), 3.84–3.81 (1H, m), 3.49–3.42 (1H, m), 2.53 (1H, ddd, *J* 9.15, 6.3, 3.15 Hz), 1.84–1.80 (1H, m), 1.72–1.68 (3H, m), 1.57–1.53 (18H, br m), 1.26 (138H, br s), 0.93 (9H, s), 0.90 (3H, d, *J* 6.6 Hz), 0.88 (3H, t, *J* 2.85 Hz), 0.87 (3H, t, *J* 2.85 Hz), 0.85 (3H, d, *J* 6.65 Hz), 0.68–0.63 (1H, m), 0.48–0.41 (1H, m), 0.21–0.09 (3H, m), 0.15 (3H, s), 0.14 (3H, m); δ_C (126 MHz, $CDCl_3$): 173.1, 73.7, 62.9, 62.8, 38.1, 37.4, 34.5, 32.0, 31.9, 31.4, 30.1, 29.7, 29.65, 29.6, 29.5, 29.46, 29.4, 29.36 (very broad), 27.4, 27.3, 26.1, 25.7, 22.7, 22.3, 19.7, 18.6, 17.9, 14.1, 10.5, 9.8, −4.3, −4.9; ν_{max}/cm^{-1}: 2923, 2853, 1708, 1465, 1377, 1259, 1119, 1082, 1027, 835, 779, 728.

*3.1.17. (R)-2-{(R)-17-[(1S,2R)-2-((1S,21S)-1,21-Dimethyl-20-oxonon atriacontyl)cyclopropyl]-1-(tert-butyldimethylsilanyloxy) heptadecyl} hexacosanoic acid methyl ester (**32**).*

(i) Pyridinium-*p*-toluene sulfonate (0.20 g, 0.79 mmol) was added to a stirred solution of acid **31** (0.90 g, 0.61 mmol) in THF (15 mL), MeOH (2 mL) and stirred at 47 °C for 18 h, when TLC showed that the reaction was almost complete. Satd aq sodium bicarbonate (3 drops) was added and the product was extracted with petrol/ethyl acetate (3×100 mL, 5:1). The combined organic layers were dried and evaporated. Column chromatography eluting with petrol/ethyl acetate (10:1) gave a white semi-solid, (*R*)-2-{(*R*)-1-(*tert*-butyldimethylsilanyloxy)-17-[(1*S*,2*R*)-2-((1*S*,20*S*,21*S*)-20-hydroxy-1,21-dimethylnonatria-contyl)cyclopropyl]heptadecyl}hexacosanoic acid (0.62 g, 73%) [Found $(M+Na)^+$: 1418.4087; $C_{93}H_{186}O_4Si$+Na requires: 1418.4018], which showed δ_H (500 MHz, $CDCl_3$): 3.82 (1H, ddd, 7.3, 5.1, 2.6 Hz), 3.50 (1H, dt, *J* 6.9, 4.8 Hz), 2.53 (1, ddd, 8.8, 6.2, 2.5 Hz), 1.73–1.68 (1H, m), 1.63–1.54 (6H, m), 1.26 (145H, v br s), 0.93 (9H, s), 0.909 (3H, d, *J* 6.6 Hz), 0.902 (3H, d, *J* 6.6 Hz), 0.87 (6H, t, *J* 7.6 Hz), 0.69–0.63 (1H, m), 0.48–0.42 (1H, m), 0.21–0.09 (2H, m), 0.15 (3H, s), 0.14 (3H, s); δ_C (126 MHz, $CDCl_3$): 172.3, 75.2, 73.7, 46.7, 38.2, 38.1, 37.4, 35.8, 34.5, 33.6, 31.9, 30.1, 30.0, 29.7, 29.65, 29.6, 29.54, 29.5, 29.4, 29.35, 27.4, 27.6, 26.3, 26.1, 25.7, 22.7, 19.7, 18.6, 17.9, 14.1, 13.6, 10.5, −4.2, −4.5; ν_{max}: 3485, 2856, 1743, 1471, 1379, 1244, 1171, 1020 cm^{-1}.

(ii) The above acid (0.53 g, 0.38 mmol) was dissolved in dichloromethane (10 mL) and added in portions to a stirred solution of PCC (24 mg, 0.11 mmol) in dichloromethane (30 mL) at room temperature. The mixture was stirred for 2 h, then diluted with petrol/ethyl acetate (20 mL, 10:1), filtered over Celite and evaporated. Column chromatography eluting with petrol/ethyl acetate (10:1) gave the title compound as a white semi-solid, **32** (0.47 g, 88%) [Found $(M+Na)^+$: 1416.3886; $C_{93}H_{184}O_4Si$+Na requires: 1416.3861], $[\alpha]_D^{21}$ +6.33 (c 0.71, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.82 (1H, ddd, *J* 7.9, 5.4, 2.6 Hz), 2.55–2.49 (1H, m), 2.41(1H, td, *J* 7.3, 2.2 Hz), 1.55 (28H, v br s), 1.26 (123H, br s), 1.06 (3H, d, *J* 6.9 Hz), 0.94 (9H, s), 0.90 (3H, d, *J* 6.2 Hz), 0.90 (6H, t, *J* 7 Hz), 0.48–0.42 (1H, m), 0.21–0.16 (1H, m), 0.16 (3H, s), 0.15 (3H, s), 0.13–0.09 (1H, m); δ_C (126 MHz, $CDCl_3$): 171.0, 38.9, 31.9, 29.73, 29.7, 29.66, 29.54, 29.5, 29.4, 29.36, 25.7, 22.7, 14.1, −4.9, −5.5; ν_{max}: 2943, 2857, 1689, 1468, 1372, 1209 cm^{-1}.

*3.1.18. (R)-2-{(R)-17-[(1S,2R)-2-((1S,21S)-1,21-Dimethyl-20-oxononatriacontyl)-cyclopropyl]-1-hydroxyheptadecyl} hexacosanoic acid (**33**).* The ester **32** (0.21 g, 0.15 mmol) was stirred in dry THF

(5 mL) in a dry polyethylene vial under nitrogen at room temperature. Pyridine (0.1 mL) and HF·Pyridine (0.6 mL) was added and the mixture was stirred for 17 h at 45 °C, then diluted with petrol/ethyl acetate (5:2, 10 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/ethyl acetate (1:1, 2×50 mL). The combined organic layers were washed with brine, dried and evaporated to give a residue. Column chromatography eluting with petrol/ethyl acetate (7:3) gave the title compound as a white solid **33** (0.16 g, 84%), $[\alpha]_D^{19}$ +10.55 (*c* 0.54, $CHCl_3$), mp 67–68 °C [Found $(M+Na)^+$: 1302.2938, $C_{87}H_{170}O_4$+Na requires: 1302.2991]. This showed δ_H (500 MHz, $CDCl_3$): 3.71 (1H, dt, *J* 7.9, 4.75 Hz), 2.38 (1H, m), 2.35–2.32 (1H, m), 2.29 (2H, td, *J* 9.45, 1.9 Hz), 1.77–1.70 (1H, m), 1.66–1.59 (2H, m), 1.56–1.46 (5H, m), 1.26 (142, br s), 1.06 (2H, d, *J* 6.95 Hz), 0.90 (2H, d, *J* 6.95 Hz), 0.88 (6H, t, *J* 6.65 Hz), 0.69–0.64 (1H, m), 0.47–0.42 (1H, m), 0.21–0.17 (1H, m), 0.16–0.08 (2H, m); δ_C (126 MHz, $CDCl_3$): 215.5, 178.5, 72.11, 50.7, 46.3, 41.2, 38.1, 37.4, 35.6, 34.5, 33.0, 31.9, 29.73, 29.7, 29.65, 29.6, 29.5, 29.47, 29.4, 29.36, 29.3, 27.32, 26.1, 23.7, 22.7, 19.7, 18.6, 16.4, 14.1, 10.5; ν_{max}: 2922, 2853, 1716, 1685, 1470, 1037 cm^{-1}.

*3.1.19. (15S,16S)-15-Methoxy-16-methyltetratriacontyl pivalate (**35**).* A solution of the aldehyde **34**[31] (1.56 g, 3.56 mmol) and the sulphone **8** (*n*=7) (1.74 g, 4.27 mmol) in dry THF (50 mL) was stirred under nitrogen at −10 °C. Lithium bis(trimethylsilyl)amide (5.24 mL, 5.56 mmol, 1.06 M) was added dropwise between −12 and −5 °C, and the solution was stirred for 18 h. Dichloromethane (50 mL) and satd aq ammonium chloride (50 mL) were added. The aqueous layer was re-extracted with further dichloromethane (2×100 mL) and the combined organic layers were dried and evaporated. Column chromatography eluting with petrol/ether (10:1) gave a colourless oil, (*E*/*Z*)-2,2-dimethylpropionic acid 15-methoxy-16-methyl-tetratriacont-7-enyl ester (1.78 g, 81%). Palladium on charcoal (0.2 g, 10%) was added to a stirred solution of the above product (1.78 g, 2.87 mmol) in THF (5 mL) and IMS (40 mL). The mixture was stirred under hydrogen at atmospheric pressure. When no more hydrogen was absorbed, the catalyst was removed through a pad of Celite and washed with THF (50 mL). The filtrate was evaporated to give the title compound as a colourless oil **35** (1.57 g, 88%), $[\alpha]_D^{22}$ −6.7 ($CHCl_3$, 1.25 μmol) [Found $(M+Na)^+$: 645.6152; $C_{41}H_{82}O_3$+Na requires: 645.6161], which showed δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.6 Hz), 3.34 (3H, s), 3.02–2.96 (1H, m), 1.66 (2H, pent, *J* 6.6 Hz), 1.55–1.28 (58H, m), 1.24 (9H, s), 1.14–1.03 (1H, m), 0.93 (3H, t, *J* 6.6 Hz), 0.90 (3H, d, *J* 7.0 Hz); δ_C (126 MHz, $CDCl_3$): 178.3, 85.5, 64.5, 57.7, 35.4, 32.4, 31.9, 30.9, 30.5, 29.92, 29.89, 29.7, 29.6, 29.5, 29.4, 29.3, 28.6, 27.6, 26.1, 26.0, 22.4, 14.8, 14.1; ν_{max}: 2935, 1749, 1134 cm^{-1}.

*3.1.20. 5-((15S,16S)-15-Methoxy-16-methyltetratriacontyl-1-sulfonyl)-1-phenyl-1H-tetrazole (**36**).*

(i) Lithium aluminium hydride (0.14 g, 3.79 mmol) was added to THF (20 mL) stirred at −20 °C under nitrogen. (15*S*,16*S*)-15-Methoxy-16-methyltetratriacontyl pivalate **35** (1.57 g, 2.52 mmol) in THF (10 mL) was added slowly and allowed to reach RT, then heated at reflux for 1 h. The reaction was cooled to −20 °C and quenched with satd aq sodium sulfate until a white precipitate formed. THF (30 mL) was added and the mixture was stirred for 30 min, then filtered through a bed of silica and the solvent evaporated. The resulting solution was taken up in dichloromethane (50 mL), washed with water (10 mL) then dried and the solvent evaporated. Column chromatography eluting with petrol/ether (20:1, then 1:1) gave a white solid, (15*S*,16*S*)-15-methoxy-16-methyltetratriacontan-1-ol (1.04 g, 79%), $[\alpha]_D^{20}$ −8.97 ($CHCl_3$, 1.22 μmol) [Found $(M+Na)^+$: 561.5584; $C_{36}H_{74}O_2$+Na requires: 561.5586], which showed δ_H (500 MHz, $CDCl_3$): 3.70 (2H, t, *J* 6.6 Hz), 3.33 (3H, s), 3.01–2.96 (1H, m), 1.66–1.64 (1H, m), 1.61 (2H, pent, *J* 6.6 Hz), 1.47 (1H, br s) 1.47–1.20 (56H, m), 1.16–1.04 (1H, m), 0.90 (3H, t, *J* 7 Hz) 0.88 (3H, d, *J* 6.6 Hz); δ_C (126 MHz, $CDCl_3$): 86.2, 63.1, 57.8, 35.6, 32.8, 32.6, 32.0, 30.7, 30.2, 30.0, 29.8, 29.7, 29.6, 29.5, 29.4, 27.5, 26.3, 25.8, 22.9, 14.9, 14.1; ν_{max}: 3376, 2929, 1103, 1080 cm^{-1}.

(ii) *N*-Bromosuccinimide (0.44 g, 2.46 mmol, 1.3 mol equiv) was added in portions over 15 min to a stirred solution of the alcohol (1.04 g, 1.89 mmol) and triphenylphosphine (0.56 g, 2.14 mmol, 1.13 equiv) in dichloromethane (20 mL) at 0 °C. The mixture was stirred at rt for 1 h, quenched with satd aq sodium *meta*-bisulfite (25 mL), then the aqueous layer was re-extracted with dichloromethane (2×20 mL) and the combined organic extracts washed with water (50 mL), dried and evaporated. The residue was treated with petrol/ether (1:1, 50 mL), refluxed for 30 min, filtered and washed with petrol/ether (1:1, 25 mL). The filtrate was evaporated. Column chromatography eluting with petrol/ether (10:1) gave a white solid, (15*S*,16*S*)-1-bromo-15-methoxy-16-methyltetratriacontane (0.76 g, 83%), $[\alpha]_D^{21}$ −7.74 ($CHCl_3$, 1.25 μmol) [Found $(M+Na)^+$: 623.4713; $C_{36}H_{73}{}^{79}BrO$ + Na requires: 623.4742], which showed δ_H (500 MHz, $CDCl_3$): 3.46 (2H, t, *J* 6.8 Hz), 3.39 (3H, s), 3.03–2.98 (1H, m), 1.91 (2H, pent, *J* 6.8 Hz), 1.71–1.65 (1H, m), 1.52–1.26 (58H, m), 0.91 (3H, t, *J* 6.4 Hz), 0.88 (3H, d, *J* 6.8 Hz); δ_C (126 MHz, $CDCl_3$): 85.8, 57.9, 35.3, 34.2, 32.9, 32.6, 31.9, 30.8, 30.3, 29.9, 29.7, 29.6, 29.52, 29.48, 29.4, 28.9, 28.4, 27.7, 26.3, 22.8, 14.9, 14.4; ν_{max}: 2943, 2868, 1123, 743 cm^{-1}.

(iii) The bromide (0.70 g, 1.14 mmol) in THF (3 mL) and acetone (3 mL) was added to a stirred solution of 1-phenyl-1H-tetrazole-5-thiol (0.22 g, 1.26 mmol, 1.1 mol equiv) and anhydrous potassium carbonate (0.55 g, 4.00 mmol, 3.5 mol equiv) in acetone (15 mL) at rt. After 18 h, the solvent was evaporated and the residue diluted with petrol/ether (1:1, 20 mL) and water (20 mL). The aqueous layer was re-extracted with petrol/ether (1:1, 2×10 mL). The combined organic extracts were dried and evaporated; column chromatography eluting with 10:1 petrol/ether gave a colourless oil, 5-((15*S*,16*S*)-15-methoxy-16-methyltetratriacontyl-1-sulfan-yl)-1-phenyl-1*H*-tetrazole (0.76 g, 93%), $[\alpha]_D^{21}$ −6.49 ($CHCl_3$, 1.11 μmol) [Found $(M+Na)^+$: 721.5784; $C_{43}H_{78}N_4OS$+Na requires: 721.5794], which showed δ_H (500 MHz, $CDCl_3$): 7.64–7.51 (5H, m), 3.39 (2H, t, *J* 7.3 Hz), 3.30 (3H, s), 2.99–2.94 (1H, m), 1.82 (2H, pent, *J* 7.4 Hz), 1.67–1.60 (1H, m), 1.49–1.20 (58H, m), 0.91 (3H, t, *J* 6.55 Hz), 0.87 (3H, d, *J* 6 Hz); δ_C (126 MHz, $CDCl_3$): 154.5, 130.1, 129.8, 123.9, 85.5, 57.7, 35.3, 30.5, 30.0, 29.6, 29.5, 29.1, 28.7, 26.2, 22.7, 14.9, 14.1; ν_{max}: 2926, 2861, 1098 cm^{-1}.

(iv) *m*-Chloroperbenzoic acid (0.52 g, 3.04 mmol, 3.0 mol equiv) in dichloromethane (5 mL) was added slowly to the tetrazole (0.72 g, 1.01 mmol) and sodium hydrogen carbonate (0.38 g, 4.56 mmol, 4.5 mol equiv) in dichloromethane (5 mL) at 5 °C. The mixture was stirred for 18 h at rt, then the solvent was evaporated and the residue was diluted with ethyl acetate (5 mL) and slowly quenched with satd aq sodium metabisulfite (2 mL). The aqueous layer was re-extracted with ethyl acetate (2×10 mL) and the combined organic extracts were washed with satd aq sodium hydrogen carbonate (10 mL) and then water (20 mL). The organic extract was then dried and evaporated. Column chromatography eluting with 1:1 petrol/ether gave the title compound as a white solid **36** (0.67 g, 89%), $[\alpha]_D^{23}$ −6.28 ($CHCl_3$, 1.02 μmol) [Found $(M+Na)^+$: 753.5674; $C_{43}H_{78}N_4O_3S$+Na requires: 753.5692], which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.70 (2H, m), 7.69–7.61 (3H, m), 3.74 (2H, t, *J* 7.9 Hz), 3.34 (3H, s), 2.97–2.95 (1H, m), 1.96 (2H, pent, *J* 7.9 Hz), 1.63–1.58 (1H, m), 1.50 (2H, pent, *J* 7.6 Hz), 1.45–1.22 (56H, m), 0.89 (3H, t, *J* 6.6 Hz), 0.85 (3H, d, *J* 6.7 Hz); δ_C (126 MHz, $CDCl_3$): 153.5, 133.1, 131.5, 130.3, 125.1, 85.5, 57.7, 56.0,

35.3, 32.4, 31.9, 30.5, 30.0, 29.9, 29.7, 29.7, 29.62, 29.60, 29.5, 29.4, 29.2, 28.9, 26.5, 22.8, 22.0, 15.1, 14.4; ν_{max}: 2947, 2852, 1321, 1164, 1097 cm^{-1}.

*3.1.21. 9-((1S,2R)-2-((S)-4-Oxobutan-2-yl)cyclopropyl)nonyl pivalate (**37**).* 9-((1*S*,2*R*)-2-((*S*)-4-Hydroxybutan-2-yl)cyclopropyl)nonyl pivalate **11** (*n*=8) (see Supplementary data) (0.42 g, 1.23 mmol) was added to a stirred suspension of PCC (0.67 g, 3.09 mmol, 2.5 mol equiv) in dichloromethane (10 mL). The mixture was stirred for 2 h at rt, then diluted with ether (50 mL). The mixture was filtered through a bed of silica and washed with ether (2×10 mL), and the solvent evaporated. Column chromatography eluting with petrol/ether (5:2) gave the title compound as a colourless oil **37** (0.39 g, 93%), $[\alpha]_D^{22}$ +20.47 ($CHCl_3$, 1.08 μmol) [Found $(M+Na)^+$: 361.2719; $C_{21}H_{38}O_3$+Na requires: 361.2718], which showed δ_H (500 MHz, $CDCl_3$): 9.78 (1H, s), 2.50 (1H, ddd, *J* 15.75, 6.3, 1.9 Hz), 2.35 (1H, ddd, *J* 15.75, 7.9, 2.5 Hz), 1.61 (2H, pent, *J* 6.6 Hz), 1.32–1.13 (26H, m), 1.00 (3H, d, *J* 6.65 Hz), 0.49 (1H, m), 0.34–0.21 (3H, m); δ_C (126 MHz, $CDCl_3$): 202.9, 178.6, 64.4, 51.4, 38.7, 34.1, 33.9, 29.6, 29.51, 29.48, 29.2, 28.6, 27.2, 25.9, 25.6, 20.0, 18.8, 11.4; ν_{max}: 2924, 2878, 1727 cm^{-1}.

*3.1.22. 9-((1S,2R)-2-((2S,19S,20S)-19-Methoxy-20-methyloctatriacontan-2-yl)cyclopropyl)nonyl pivalate (**38**).* Lithium hexamethyldisilazide (0.92 mL, 0.98 mmol, 1.06 M) was added dropwise to a stirred solution of sulfone **36** (670 mg, 0.90 mmol) and the aldehyde **37** (255 mg, 0.752 mmol) in dry THF (10 mL) under nitrogen at −20 °C. The temperature rose to −10 °C during the addition of the base, and a yellow solution resulted. The mixture was allowed to reach rt and was stirred for 1 h, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 mL). The product was extracted with petrol/ether (1:1, 3×10 mL). The combined organic layers were washed with brine (20 mL), dried and evaporated to give an oil, which was purified via column chromatography eluting with petrol/ether (20:1) to give 9-((1*S*,2*R*)-2-[(*E*/*Z*)-(2*S*,19*S*,20*S*)-19-methoxy-20-methyloctatriacont-4-en-2-yl]cyclopropyl)nonyl pivalate (410 mg, 54%). Dipotassium azodicarboxylate (2.49 g, 12.83 mmol, 30 mol equiv) was added to a stirred solution of the above (410 mg, 0.487 mmol) in THF (20 mL) and methanol (10 mL) at 10 °C under nitrogen, giving a yellow precipitate. Glacial acetic acid (1 mL) in THF (2 mL) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C and poured slowly into satd aq sodium hydrogen carbonate (5 mL) and then extracted with petrol/ether (1:1, 3×25 mL). The combined organic layers were washed with water (10 mL), dried and evaporated to give a thick oil, which slowly solidified. Column chromatography eluting with 10:1 petrol/ether gave the title compound as a colourless oil **38** (400 mg, 97%), $[\alpha]_D^{21}$ −6.85 ($CHCl_3$, 0.87 μmol) [Found $(M+Na)^+$: 867.8511; $C_{57}H_{112}O_3$+Na requires: 867.8509], which showed δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.65 Hz), 3.70 (1H, m), 3.35 (3H, s), 1.60 (9H, s), 1.44–1.19 (84H, br m including br s at 1.26), 0.92–0.84 (10H, m), 0.47–0.44 (1H, m), 0.22–0.18 (1H, m), 0.17–0.14 (1H, m), 0.13–0.09 (1H, m); δ_C (126 MHz, $CDCl_3$): 85.5, 65.8, 63.1, 57.7, 38.1, 35.4, 34.5, 32.8, 32.4, 31.9, 30.5, 30.1, 30.0, 29.9, 29.7, 29.6, 29.5, 29.4, 27.6, 27.3, 26.2, 26.1, 25.8, 22.7, 19.7, 18.6, 15.3, 14.9, 14.1, 10.5; ν_{max}: 2918, 2857, 1745 cm^{-1}

*3.1.23. 9-((1R,2R)-2-((2S,19S,20S)-19-Methoxy-20-methyloctatriacontan-2-yl)cyclopropyl)nonanal (**39**).*

(i) Lithium aluminium hydride (36.0 mg, 0.95 mmol, 2 mol equiv) was added to stirred THF (5 mL, HPLC grade) at −20 °C under nitrogen. A solution of pivalate **38** (400 mg, 0.474 mmol) in THF (5 mL, HPLC grade) was added slowly and then the reaction was allowed to reach rt, refluxed for 1 h, cooled to −20 °C, then quenched with satd aq sodium sulfate until a white precipitate formed. The mixture was stirred for 30 min and then filtered through silica and the solvent evaporated. Column chromatography eluting with petrol/ether (1:1) gave a colourless oil, 9-((1*S*,2*R*)-2-((2*S*,19*S*,20*S*)-19-methoxy-20-methyloctatriacontan-2-yl)cyclopropyl)nonan-1-ol (260 mg, 72%), $[\alpha]_D^{19}$ −6.11 ($CHCl_3$, 1.08 μmol) [Found $(M+Na)^+$: 783.7984; $C_{52}H_{104}O_2$+Na requires: 783.7934], which showed δ_H (500 MHz, $CDCl_3$): 4.03 (2H, t, *J* 6.65 Hz), 3.69 (1H, m), 3.35 (3H, s), 1.52–1.20 (84H, br m including br s at 1.26), 0.90–0.82 (10H, m), 0.46–0.44 (1H, m), 0.22–0.18 (1H, m), 0.17–0.14 (1H, m), 0.13–0.09 (1H, m); δ_C (126 MHz, $CDCl_3$): 85.5, 63.1, 57.7, 38.1, 37.4, 35.4, 34.5, 32.8, 32.4, 31.9, 30.5, 30.0, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 27.3, 26.2, 25.8, 22.7, 19.7; ν_{max}: 3343, 2975, 2847 cm^{-1}.

(ii) The alcohol (0.260 g, 0.343 mmol) was added to a stirred suspension of PCC (0.22 g, 1.03 mmol, 3 mol equiv) in dichloromethane (10 mL). After 1 h at rt, it was diluted with ether (10 mL). The mixture was filtered through a bed of silica and washed with ether (2×5 mL), and the solvent evaporated. Column chromatography eluting with 10:1 petrol/ether gave a colourless oil, 9-((1*R*,2*R*)-2-((2*S*,19*S*,20*S*)-19-methoxy-20-methyloctatriacontan-2-yl)cyclopropyl)nonanal **39** (0.24 g, 96%), $[\alpha]_D^{19}$ −3.45 ($CHCl_3$, 1.25 μmol) [Found $(M+Na)^+$: 781.7756; $C_{52}H_{102}O_2$+Na requires: 781.7777], which showed δ_H (500 MHz, $CDCl_3$): 9.77 (1H, br t, *J* 1.85 Hz), 3.38 (3H, s), 2.97–2.95 (1H, m), 2.43 (2H, dt, *J* 1.85, 7.55 Hz), 1.99–1.97 (1H, m), 1.65–1.61 (1H, m), 1.56 (2H, m), 1.40–1.09 (78H, br m including br s at 1.27), 0.89 (6H, dt, *J* 2.85, 6.6 Hz), 0.85 (3H, d, *J* 6.6 Hz), 0.48–0.43 (1H, m), 0.22–0.18 (1H, m), 0.17–0.14 (1H, m), 0.13–0.09 (1H, m); δ_C (126 MHz, $CDCl_3$): 205.1, 85.5, 65.6, 57.7, 43.9, 38.1, 37.4, 35.4, 34.4, 32.8, 32.4, 31.9, 30.5, 30.0, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 27.3, 26.2, 25.8, 22.7, 19.7, 18.6, 16.5, 14.3, 10.5; ν_{max}: 2984, 2875, 1724 cm^{-1}.

*3.1.24. Methyl 2-((1R,2R)-1-(tert-butyldimethylsilyloxy)-19-((1S,2R)-2-((2S,18S,19S)-18-methoxy-19-methylheptatriacontan-2-yl)cyclopropyl)nonadecyl)hexacosanoate (**41**).* Lithium hexamethyldisilazide (0.29 mL, 0.31 mmol, 1.06 M) was added dropwise to a stirred solution of sulfone **40** (183 mg, 0.206 mmol) (see Supplementary data) and aldehyde **39** (172 mg, 0.227 mmol) in dry THF (10 mL) under nitrogen at −20 °C. The temperature rose to −10 °C during the addition of the base, and a yellow solution resulted. The mixture was allowed to reach rt and was stirred for 1 h, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 mL). The product was extracted with petrol/ether (1:1, 3×10 mL). The combined organic layers were washed with brine (20 mL), dried and evaporated to give an oil. Column chromatography eluting with 20:1 petrol/ether gave methyl 2-((*R*)-(*E*/*Z*)-1-(*tert*-butyl-dimethylsilyloxy)-19-((1*S*,2*R*)-2-((2*S*,18*S*,19*S*)-18-methoxy-19-methylheptatriacontan-2-yl)cyclopropyl)-nonadec-10-enyl)hexacosanoate (80.6 mg, 28%). Dipotassium azodicarboxylate (0.33 g, 1.7 mmol, 30 mol equiv) was added to a stirred solution of the above compound (80.6 mg, 0.057 mmol) in THF (5 mL) and methanol (5 mL) at 10 °C under nitrogen, giving a yellow precipitate. Glacial acetic acid (1 mL) in THF (2 mL) was added over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C, poured slowly into satd aq sodium hydrogen carbonate (5 mL), then extracted with petrol/ether (1:1, 3×10 mL). The combined organic layers were washed with water (10 mL), dried and evaporated to give a thick oil, which slowly solidified. Column chromatography eluting with 10:1 petrol/ether gave the title compound as a waxy white solid, **41** (75.7 mg, 94%), $[\alpha]_D^{24}$ −1.45 ($CHCl_3$, 0.86 μmol) [Found $(M+Na)^+$: 1446.21; $C_{95}H_{190}O_4Si$+Na requires: 1446.43], which showed δ_H (500 MHz, $CDCl_3$): 3.92–3.90 (1H, m), 3.66 (3H, s), 3.35 (3H, s), 2.97–2.95 (1H, m), 2.54 (1H, ddd, *J* 3.75, 7.25, 11 Hz), 1.58–1.18 (150H, br m including br s at 1.27), 0.91–0.85 (21H, m), 0.48–0.44 (1H, m), 0.22–0.18 (1H, m), 0.17–0.14 (1H, m), 0.13–0.09 (1H, m), 0.05 (3H, s), 0.03 (3H, s); δ_C

(126 MHz, $CDCl_3$): 175.1, 125.5, 85.5, 73.2, 65.9, 57.7, 51.6, 38.1, 37.4, 37.1, 35.8, 35.4, 34.5, 33.7, 32.8, 32.4, 31.9, 31.1, 30.5, 30.3, 30.1, 30.0, 29.9, 29.8, 29.7, 29.64, 29.60, 29.52, 29.49, 29.4, 27.8, 27.6, 27.5, 27.3, 26.2, 26.1, 25.8, 23.7, 22.7, 19.7, 18.6, 18.0, 14.9, 14.1, 10.5, −4.4, −4.9; ν_{max}: 2923, 2852, 1741, 1465 cm^{-1}.

*3.1.25. (R)-2-((R)-1-Hydroxy-19-((1S,2R)-2-((2S,18S,19S)-18-methoxy-19-methylheptatriacontan-2-yl)cyclopropyl)nonadecyl)hexacosanoic acid (**42**).*

(i) A dry polyethylene vial equipped with a rubber septum was charged with ester **41** (0.070 g, 0.049 mmol) in dry THF (4 mL) under nitrogen at 0 °C. Pyridine (0.2 mL) and hydrogen fluoride–pyridine complex (0.20 mL, 0.14 mmol, 210 mol equiv) were added and the mixture stirred for 32 h at 43 °C, then slowly poured into satd aq sodium hydrogen carbonate (10 mL) until no more carbon dioxide was liberated. The product was extracted with petrol/ether (1:1, 3×50 mL), dried and evaporated to give a solid. Column chromatography eluting with 4:1 petrol/ether gave a white solid, methyl 2-((*R*)-1-hydroxy-19-((1*S*,2*R*)-2-((2*S*,18*S*, 19*S*)-18-methoxy-19-methylheptatriacontan-2-yl) cyclopropyl)-nonadecyl)-hexacosanoate (35 mg, 54%), $[\alpha]_D^{23}$ −1.12 ($CHCl_3$, 0.99 μmol), mp 63–65 °C [Found $(M+Na)^+$: 1332.19; $C_{89}H_{176}O_4$+Na requires: 1332.35], which showed δ_H (500 MHz, $CDCl_3$): 3.72 (3H, s), 3.69–3.64 (1H, m), 3.35 (3H, s), 2.97–2.95 (1H, m), 2.44 (1H, dt, *J* 5.35, 9.15 Hz), 1.63–1.13 (150H, br m including br s at 1.26), 0.91–0.85 (12H, m), 0.47–0.43 (1H, m), 0.22–0.18 (1H, m), 0.17–0.14 (1H, m), 0.13–0.09 (1H, m); δ_C (126 MHz, $CDCl_3$): 176.2, 85.5, 72.3, 57.7, 51.5, 50.9, 38.1, 37.4, 35.7, 35.3, 32.4, 31.9, 31.6, 30.5, 30.3, 30.1, 29.9, 29.7, 29.64, 29.62, 29.60, 29.58, 29.53, 29.49, 29.42, 29.38, 27.6, 27.4, 27.3, 26.2, 26.1, 25.7, 22.7, 19.7, 18.6, 15.3, 14.9, 14.1, 10.5; ν_{max}: 3509, 2916, 2848, 2360, 2341, 1727, 1714, 1468 cm^{-1}.

(ii) Lithium hydroxide monohydrate (20 mg, 0.84 mmol, 30 mol equiv) was added to a stirred solution of the ester (35 mg, 0.027 mmol) in THF (2.5 mL), methanol (0.3 mL) and water (0.3 mL) at rt. The mixture was stirred at 43 °C for 18 h, then cooled to rt and acidified with hydrochloric acid (5%, 1 mL) and the aqueous layer extracted with warm petrol/ether (1:1, 3×10 mL). The combined organic extracts were dried and evaporated. Column chromatography eluting with 5:1 petrol/ethyl acetate gave the title compound as a waxy white solid, **42** (24.0 mg, 69%), $[\alpha]_D^{22}$ −0.97 ($CHCl_3$, 0.47 μmol) [Found $M+Na^+$: 1318.24; $C_{88}H_{174}O_4$+Na requires: 1318.33], which showed δ_H (500 MHz, $CDCl_3$): 3.74–3.70 (1H, m), 3.36 (3H, s), 2.99–2.96 (1H, m), 2.49–2.45 (1H, m), 1.79–1.72 (1H, m), 1.69–1.61 (2H, br m), 1.55–1.10 (149H, br m including br s at 1.27), 0.91–0.85 (12H, br m including t, *J* 6.95 Hz), 0.48–0.43 (1H, m), 0.22–0.18 (1H, m), 0.17–0.14 (1H, m), 0.13–0.09 (1H, m); δ_C (126 MHz, $CDCl_3$): 178.7, 85.6, 72.1, 57.7, 50.6, 38.1, 37.4, 35.6, 35.3, 34.5, 32.3, 31.9, 30.5, 30.1, 30.0, 29.9, 29.73, 29.7, 29.6, 29.5, 29.4, 29.36, 27.6, 27.3, 27.25, 26.2, 26.14, 25.7, 22.69, 19.7, 18.6, 14.9, 14.1, 10.5; ν_{max}: 3520, 2924, 2853, 1735, 1465 cm^{-1}.

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Supplementary data

Proton and carbon NMR spectra and additional experimental detail are provided. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.04.134.

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