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The Synthesis of Single Enantiomers of α-Mycolic Acids of *Mycobacterium tuberculosis* and Related Organisms, with Alternative Cyclopropane Stereochemistries

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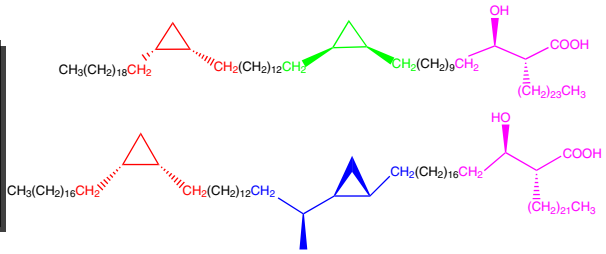
Three stereoisomers of a mycolic acid containing two *cis*-cyclopropanes, and two stereoisomers of a *trans*-cyclopropane containing mycolic acid are obtained by coupling single enantiomers of the three coloured fragments using the black carbon chains in multi-step sequences



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Abstract We report the synthesis of three stereoisomers of a mycolic acid from *Mycobacterium tuberculosis* containing a di-*cis*-cyclopropane and of two stereoisomers of a mycolic acid containing a proximal *trans*-cyclopropane and a distal *cis*-cyclopropane.

Key words mycolic acid, *cis*-cyclopropane, *trans*-cyclopropane, stereoisomers

Mycolic acids (MA) from mycobacteria, having a general structure **1** (Figure 1), usually containing 70 to 90 carbons, are present as complex mixtures with varying chain lengths and a number of combinations of distal and proximal substituents X and Y, and different exact compositions depending on the species.[1–7]

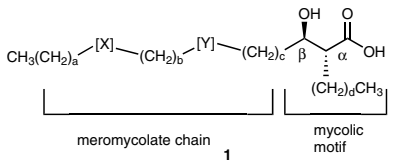
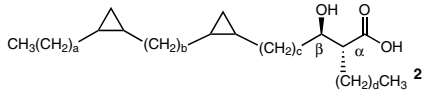


Figure 1 General structure of mycolic acids

Commonly, group Y is a *cis*- or α-methyl substituted *trans*-cyclopropane, a *cis*-alkene or a *trans*-alkene with an adjacent methyl substituent. Group X is a *cis*-cyclopropane (α- and α′-MA), a -CHMeCHOMe- fragment (methoxy-MA) or a -CHMeCO- fragment (keto-MA). Structural assignment has often been based on mass spectra of mixtures of homologues or fragments from them.[8,9] It is often difficult from the early literature to judge the certainty with which a structure has been assigned or, indeed, which actual values of *a*–*d* have been determined. However, recent detailed studies have clarified the situation considerably.[8,9] The presence and proportion of individual classes of MA, and in particular cyclopropanated MA, is known to be important for the virulence of diseases such as tuberculosis.[10–13] The free MA are themselves strongly bioactive and indeed synthetic MA of different classes, matching the structures of components of natural mixtures, are selectively active.[14]

Among the most abundant of these acids are α-MAs containing two *cis*-cyclopropanes (**2**).[8,9] The acid **2** (*a* = 19, *b* = 14, *c* = 11, *d* = 23) was reported by Minnikin and Polgar to be the major MA of *Mycobacterium tuberculosis* var *hominis*.[15] (Figure 2)

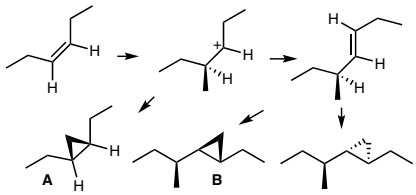


a = 15, 17, 18, 19; b = 14, 16; c = 11, 15, 17, 19, 21; d = 21, 23

Figure 2 Typical α-mycolic acid chain lengths

Indeed, such α-MA make up around 50% of the MA isolated from Mtb cells.[7] Although the hydroxy-acid grouping is known to be of *R*,*R*-configuration, the absolute stereochemistries of the cyclopropanes are not always clearly defined. There is evidence that the 1-methyl-2-methoxy unit at the distal position from the hydroxy acid in methoxy-MA is *S*,*S*,[16,17] while the corresponding carbon bearing a methyl group in ketomycolates is also *S*.[18] Much is now known about the enzymes controlling the biosynthesis of MA,[19–23] and it has been proposed, for example, that the *cis*-cyclopropane unit, the α-methyl-*trans*-cyclopropane and the α-methyl-β-alkoxy unit are formed from a *Z*-alkene through a common intermediate (Scheme 1).[24,25] A consequence of

this would be that the three subunits should have a common absolute stereochemistry at the carbon bearing the methyl group and C-1 of the *cis*-cyclopropane.



Scheme 1 Proposed common formal intermediate cation in MA biosynthesis

The stereochemistry B of the *trans*-cyclopropane unit is consistent with NMR spectra and optical rotations of this fragment in methoxy-MA,[26] and with that of the distal position in methoxy- and keto-MA, and on this basis the *cis*-cyclopropane stereochemistry is likely to be A. However, there is little direct evidence that this is the case, and an alternative possibility is that the *cis*-isomer is produced with an alternative stereochemistry in the enzyme-promoted cyclopropanation, or indeed that a mixture of stereoisomers is produced. Although the isomer with stereochemistry A at both cyclopropanes, compound **2a** (Figure 3) was reported some time ago,[27,28] and has been shown to have significant biological activity in a number of contexts,[14,29] we now describe the synthesis of the three other stereoisomers of **2** containing two *cis*-cyclopropanes in order that their biological properties may be compared to those of **2a**.

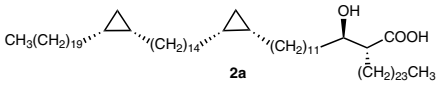
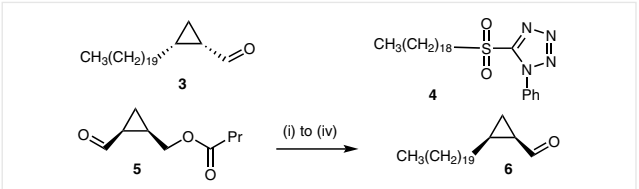


Figure 3 First synthetic α-mycolic acid

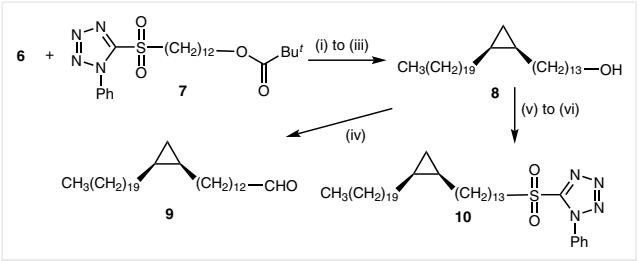
The synthetic method used, a simple extension of the method used to prepare **2a**, involved the use of a common precursor for the two chiral cyclopropane units, with C–C bonds being created at the positions shown in Figure 4.

The (1*S*,2*R*)-aldehyde **3** was prepared by a method described earlier from (1*S*,2*R*)-butyryloxymethyl-2-formylcyclopropane.[28,30,31] Reaction of (1*R*)-butyryloxymethyl-(2*S*)-formyl-cyclopropane **5** with sulfone **4** in a similar way (Scheme 2) led to the (1*R*,2*S*)-aldehyde **6**.



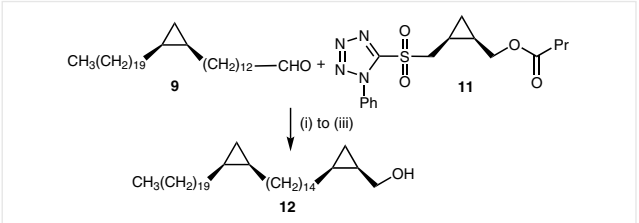
Scheme 2 *Reagents and conditions*: (i) **4**, LiHMDS, THF (80%); (ii) $LiAlH_4$, THF (90%); (iii) N_2H_4, $NaIO_4$, AcOH, $CuSO_4$, ^iPrOH (83%); (iv) PCC, CH_2Cl_2 (90%).

The aldehyde **6** was homologated to give **8** by reaction with sulfone **7** and base, again to give a mixture of *E*-and *Z*-alkenes, followed by reduction to the corresponding alcohols, hydrogenation of the alkenes using di-imide, and then oxidation to the aldehyde **9**, or converted into the sulfone **10** (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) LiHMDS, THF (98%); (ii) $LiAlH_4$, THF (91%); (iii) N_2H_4, $NaIO_4$, AcOH, $CuSO_4$, ^iPrOH (75%); (iv) PCC, CH_2Cl_2 (84%) (v) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, DEAD (97%); (vi) 3-chloroperoxybenzoic acid, $NaHCO_3$ CH_2Cl_2 (67%).

The proximal cyclopropane unit **11**[32,33] was treated with aldehyde **9** in a modified Julia reaction,[21] to give a 1:1 mixture of *E*- and *Z*-alkenes. Reduction of the esters to the corresponding alcohols using lithium aluminium hydride, followed by hydrogenation of the alkene, again using di-imide, gave a single enantiomer of alcohol **12** (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) LiHMDS, THF (65%); (ii) $LiAlH_4$, THF (89%); (iii) N_2H_4, $NaIO_4$, AcOH, $CuSO_4$, ^iPrOH (63%).

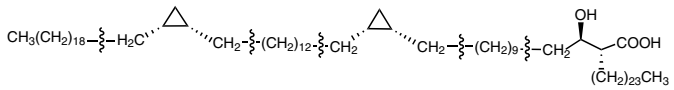
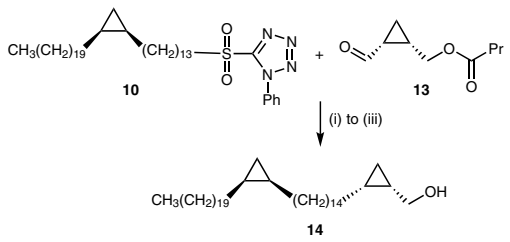


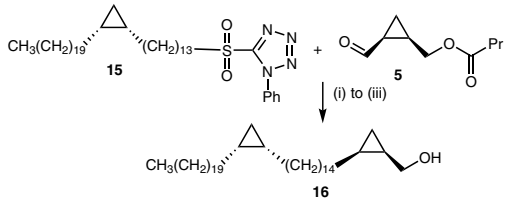
Figure 4 Fragments of MA linked in synthesis

Sulfone **10** was coupled to aldehyde **13** prepared as before,[33,34] followed again by reduction of the derived *E*/*Z*-mixture of esters to the corresponding alcohols and then saturation of the alkenes (Scheme 5).



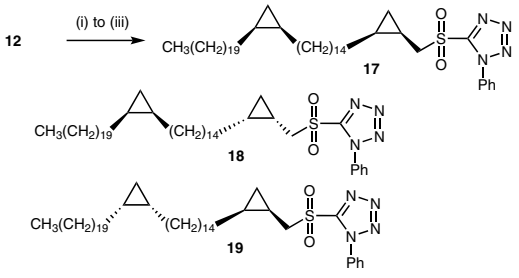
Scheme 5 *Reagents and conditions*: (i) LiHMDS, THF (62%); (ii) $LiAlH_4$, THF (72%); (iii) N_2H_4, $NaIO_4$, AcOH, $CuSO_4$, ^iPrOH (71%).

The fourth stereoisomer (**16**) was prepared by a similar method using **15** (prepared in a similar way to **10**; see the Supporting Information) and the aldehyde **5** (Scheme 6).



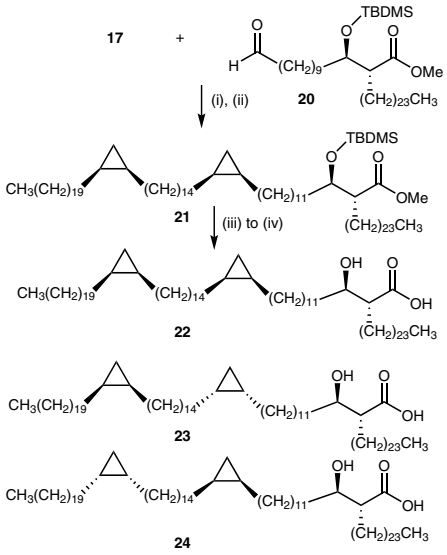
Scheme 6 *Reagents and conditions*: (i) LiHMDS, THF (78%); (ii) $LiAlH_4$, THF (50%); (iii) N_2H_4, $NaIO_4$, AcOH, $CuSO_4$, ^iPrOH (63%).

Each of the alcohols **12**, **14** and **16** was then converted into the corresponding sulfone **17**, **18** and **19** (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) 1-phenyl-1*H*-tetrazole-5-thiol, PPh_3, diethyl azodicarboxylate (93%); (ii) 3-chloroperoxybenzoic acid, $NaHCO_3$ CH_2Cl_2 (85%).

Coupling of these with the protected hydroxy-acid fragment **20**, followed by hydrogenation of the derived alkenes and then deprotection, led to the three stereoisomers, **22**, **23** and **24** (Scheme 8).

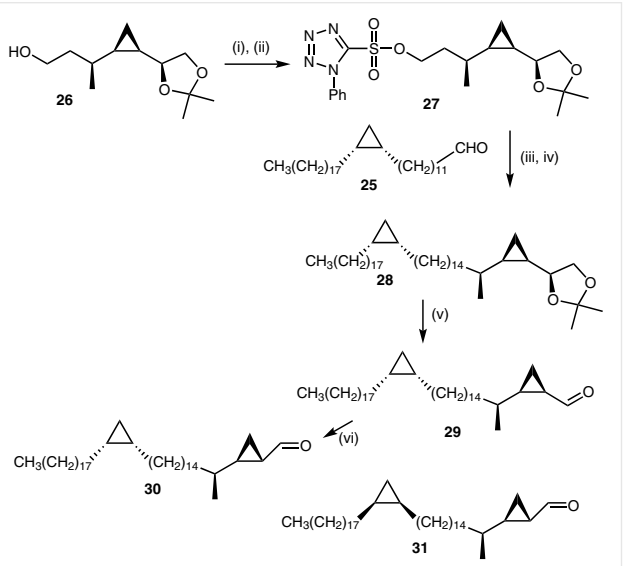


Scheme 8 *Reagents and conditions*: (i) LiHMDS, THF (87%); (ii) KOOCN=NCOOK, AcOH/MeOH/THF (86%); (iii) HF-pyridine, pyridine, THF (76%); (iv) $LiOH{\cdot}H_2O$, MeOH/THF/H_2O (93%).

The ^1H and ^{13}C NMR spectra of all four acids were essentially identical to those of a sample extracted from *M. tuberculosis*. The natural mixture was protected as the acetate on the alcohol and a methyl ester ($[\alpha]_D$ +3.7),[27] as a mixture of homologues in which **2** predominates. The specific rotation of the synthetic material **2a**, protected in the same way ($[\alpha]_D$ +4.2) was close to that of the natural mixture. The specific rotation of the synthetic free acid **2a** was $[\alpha]_D$ +2.1; the rotation is dominated by the chirality of the hydroxy acid part of the molecule and not indicative of the chirality of the *cis*-cyclopropanes, which contribute very little. Thus, the three isomers prepared in this work showed specific rotations of +2.0 (**22**), +2.5 (**23**) and +2.5 (**24**).

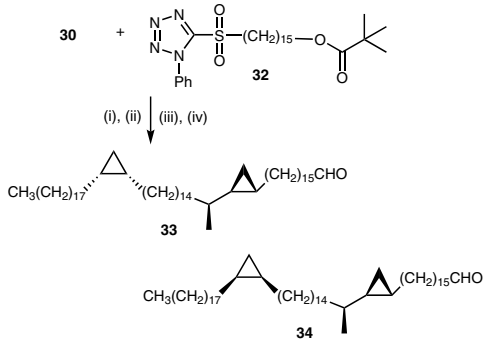
MA containing *trans*-cyclopropanes at the position in the chain closest to the hydroxy-acid are reported to have a particular effect on the cell wall and therefore on the sensitivity of mycobacterial species to hydrophobic antibiotics.[5] A purified trehalose ester of MA lacking *trans*-cyclopropane rings is five times more potent in stimulating macrophages, and is important as a suppressor of Mtb induced inflammation and virulence.[10] The biosynthesis apparently involves conversion of a *cis*-alkene into an α-methyl-*trans*-alkene caused by MmaS1 and SAM. This is then cyclopropanated by the CmaA2 gene, again with SAM, to give the α-methyl-*trans*-cyclopropane.[21–25] Inactivation of CmaA2 causes the accumulation of unsaturated derivatives in both methoxy- and keto-MA and the lack of *trans*-cyclopropanes.[26] Although α-MA containing a proximal *trans*-cyclopropane and a distal *cis*-cyclopropane do not appear to be present in Mtb, they are present in other Mycobacteria such as *Mycobacterium kansasii* and *Mycobacterium avium* complex.[8]

We therefore describe the synthesis of two stereoisomers of one such compound. The aldehyde **25**[28] was coupled to sulfone **27** (see the Supporting Information) in a modified Julia–Kocienski reaction, followed by saturation of the derived mixture of alkenes with di-imide to give **28**, and then oxidative cleavage of the acetal to produce the *cis*-aldehyde **29**. Treatment with base isomerised this to the *trans*-cyclopropane aldehyde **30**. The corresponding aldehyde **31** was prepared by a similar sequence (Scheme 9).

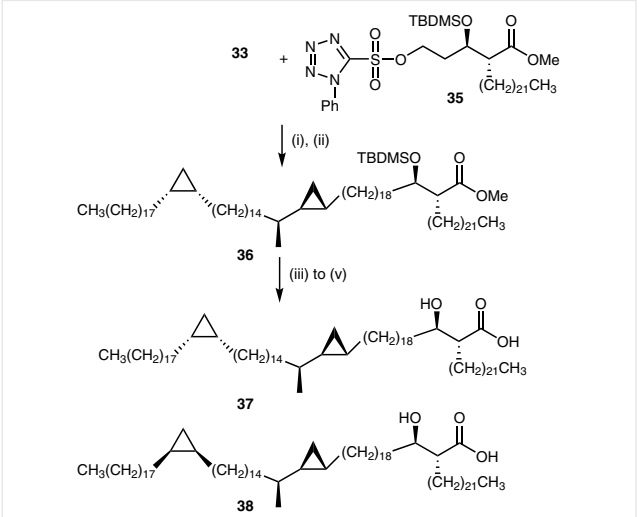


Scheme 9 *Reagents and conditions*: (i) DEAD, Ph_3P, 1-phenyl-1*H*-tetrazole-5-thiol (91%); (ii) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS/THF (87%); (iii) **25**, LiHMDS, THF (78%); (iv) KOOCN=NCOOK, AcOH, MeOH, THF (84%); (v) HIO_4, ether (83%); (vi) NaOMe, MeOH/THF, reflux, 56 h (77%).

Chain extension of the two aldehydes by standard methods provided the aldehydes **33** and **34** (Scheme 10), which were then coupled to sulfone **35**[35] to provide, after hydrolysis of the protecting groups, the free MA **37** and **38** (Scheme 11).



Scheme 10 *Reagents and conditions*: (i) LiHMDS, **32**, THF (94%); (ii) KOOCN=NCOOK, AcOH, MeOH, THF (73%); (iii) KOH, THF/MeOH/H_2O (60%); (iv) PCC, CH_2Cl_2 (85%).



Scheme 11 *Reagents and conditions*: (i) LiHMDS, THF (85%); (ii) KOOCN=NCOOK, AcOH, MeOH, THF (83%); (iii) HF-pyridine complex, pyridine (72%); (iv) LiOH, THF, MeOH, H_2O (70%); (v) imidazole, TBDMSCl, 4-DMAP; K_2CO_3, THF, MeOH, H_2O then K_2HSO_4 (85%).

The effects of the four stereoisomeric MAs **2a** and **22**–**24** in stimulating T-cells have recently been reported. Rather surprisingly, mycolic acid **24** is somewhat more stimulatory than **2a**, both having a somewhat stronger effect than **22**, with **23** having the least effect.[36] The *trans*-cyclopropane **38** is moderately stimulatory, while **37** has a smaller effect.

MA are present both as bound tetramycolyl penta-arabinose clusters and as extractable trehalose 6,6′-dimycolates ('cord factor').[2–7] The MA **37** and **38** were converted into the corresponding TDM and TMM (see the the Supporting Information) using methods described before.[37] The effects of the resulting TDMs and TMMs, and those derived from acid **22** in activating bone marrow dendritic cells to produce proinflammatory cytokines (IL-6 and TNF-α) and reactive oxygen species has recently been reported.[38] Moreover, they are recognised by antibodies in the serum of patients with pulmonary tuberculosis, providing the basis of a diagnostic assay.[39]

Chemicals used were obtained from commercial suppliers or prepared from them by methods described. Solvents which had to be dry, for example diethyl ether and tetrahydrofuran were dried over sodium wire. Petroleum was of boiling point 40–60 °C. Reactions under inert conditions were carried out under a slow stream of nitrogen. Reactions carried out at low temperatures were cooled using a bath of methylated spirit with liquid nitrogen. Silica gel (Merck 7736 silica gel) and silica plates used for thin-layer and column chromatography were obtained from Aldrich. Organic solutions were dried over anhydrous magnesium sulfate. IR spectra were carried out with a Perkin–Elmer 1600 FTIR spectrometer as liquid films. NMR spectroscopy was carried out with Bruker Avance 400 or 500 spectrometers. $[\alpha]_D$ values were recorded in $CHCl_3$ with a POLAAR 2001 Optical Activity polarimeter. Mass spectra were recorded with a Bruker-MALDI-TOF MS

instrument (to an accuracy of 1 d. p.); accurate mass values were obtained in Bangor with a Bruker Microtof LC-MS or by the EPSRC MS service in Swansea or in Bristol University.

(1*R*,2*S*)-2-Eicosylcyclopropanecarbaldehyde (6)

(a) 5-(Nonadecyl-1-sulphonyl)-1-phenyl-1*H*-tetrazole **4** (15.0 g, 0.032 mol) and butyric acid (1*R*,2*S*)-(*cis*-2-formylcyclopropyl) methyl ester **5** (4.8 g, 0.282 mol)[28] were dissolved in anhydrous THF (250 mL) and cooled to –10 °C. LiHMDS (38.6 mL, 0.041 mol) was carefully added and the mixture was stirred for 1.5 h, then water (100 mL) was added. The aqueous layer was separated and extracted with petrol/ether (1:1, 3 × 50 mL) and the combined organic layers were washed with brine (2 × 100 mL), dried and evaporated to obtain a residue; column chromatography, eluting with petrol/EtOAc (20:1) gave butyric acid (*E*/*Z*)-(1*R*,2*S*)-*cis*-2-eicos-1-enylcyclopropyl-methyl ester (9.5 g, 80 %) a colourless oil, as a mixture of isomers in ratio 2.5:1. The derived ester (8.5 g, 0.020 mol) in THF (50 mL) was gradually added to a stirred suspension of lithium aluminium hydride (1.3 g, 0.034 mol) in THF (50 mL) placed in a cooling bath, in order to control the exothermic reaction. The reaction was heated at reflux at 100 °C for 2 h, then cooled and quenched with freshly prepared sat. aq. sodium sulfate decahydrate (30 mL), stirred until a white precipitate was formed and then filtered through a bed of Celite washing with THF (3 × 50 mL). The filtrate was evaporated and the crude product was purified by column chromatography eluting with petrol/EtOAc (5:2) to give (*E*/*Z*)-(1*R*,2*S*)-*cis*-2-eicos-1-enylcyclo-propylmethanol (6.4 g, 90%) as a thick colourless oil. Hydrazine hydrate (80 mL), glacial acetic acid (5 mL) and sat. aq. copper sulphate (5 mL) were added in succession to the above alkenes (6.0 g, 0.017 mol) in 2-propanol (200 mL) at 70–80 °C. Subsequently, sodium (meta)periodate (73.4 g, 0.343 mol) in hot water was added dropwise over a period of 2 h, maintaining the temperature at 70–80 °C. The reaction was stirred for 1 h at r.t. and then quenched with sat. aq. ammonium chloride (100 mL). The aqueous layer was extracted with petrol/EtOAc (1:1, 3 × 150 mL) and the combined organic layers were washed with brine, dried and evaporated, and the product was recrystallised from petrol to give (1*R*,2*S*)-2-eicosylcyclpropyl methanol.

Yield: 5.0 g (83%); white solid; mp 57–59 °C; $[\alpha]_D^{26}$ +12 (*c* 1.1, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{48}ONa$: 375.3602; found: 375.3645.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.65 (dd, *J* = 7.2, 11.0 Hz, 1 H), 3.58 (dd, *J* = 7.9, 11.0 Hz, 1 H,), 1.67 (br s, 1 H), 1.50–1.38 (m, 4 H), 1.32–1.2 (m, 35 H), 1.15–1.09 (m, 1 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 0.69 (dt, *J* = 4.7, 8.2 Hz, 1 H), –0.01 (q, *J* = 5.2 Hz, 1 H)

^{13}C NMR (126 MHz, $CDCl_3$): δ = 63.5, 32.0, 30.5, 29.9, 29.8, 29.5, 28.6, 22.8, 18.5, 16.3, 14.0, 10.0.

IR: 3313, 1463, 1377, 1040, 1008, 720 cm^{-1}.

(c) The above alcohol (5.0 g, 14 mmol) in dichloromethane (80 mL) was added to a stirred suspension of pyridinium chlorochromate (7.6 g, 35 mmol, 2.5 mol equiv) in dichloromethane (200 mL) at r.t. The mixture was stirred for 2 h at r.t., then diluted with ether/petrol 2:1 (300 mL), then filtered through a pad of silica and Celite, washed well with ether (2 × 100 mL) and evaporated to give a white solid, which was purified by column chromatography on silica eluting with petrol/ether 2:1 to give the title compound **6**.

Yield: 4.5 g (91%); $[\alpha]_D^{26}$ +3.8 (*c* 1.1, $CHCl_3$) (enantiomer –3.9 (*c* 1.1, $CHCl_3$)).[28]

^1H NMR (500 MHz, $CDCl_3$): δ = 9.37 (d, *J* = 5.4 Hz, 1 H), 1.89–1.83 (m, 1 H), 1.62–1.55 (m, 2 H), 1.53–1.46 (m, 2 H), 1.43–1.2 (m, 36 H), 1.19 (m, 1 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.8, 31.9, 30.0, 29.7, 29.64, 29.6, 29.5, 29.4, 29.33, 29.3, 28.2, 27.8, 26.9, 24.8, 23.0, 22.7, 17.7, 14.8, 14.4, 14.1.

IR: 2921, 2851, 1700, 1465, 1215, 758, 470, 457, 441 cm^{-1}.

13-((1*R*,2*S*)-*cis*-2-Eicosylcyclopropyl)tridecan-1-ol (8)

LiHMDS (18.2 mL, 19.3 mmol) was added to a stirred solution of (1*R*,2*S*)-2-eicosylcyclopropanecarbaldehyde **6** (4.0 g, 11 mmol) and 2,2-dimethylpropanoic acid 12-(1-phenyl-1*H*-tetrazole-5-yl-sulfonyl)dodecyl ester **7** (7.10 g, 14.9 mmol)[40] in anhydrous THF (200 mL) at –10 °C under nitrogen. The mixture was allowed to reach r.t., stirred for 2 h, then the reaction was quenched with sat. aq. ammonium chloride (200 mL), the aqueous layer was separated and extracted with petrol/ether (1:1, 3 × 200 mL). The combined organic layers were dried and concentrated and the residue was purified by column chromatography, eluting with petrol/ether (20:1) to give 2,2-dimethylpropionic acid (*E*/*Z*)-13-((1*R*,2*S*)-*cis*-2-eicosylcyclopropyl)tridec-12-enyl ester (6.6 g, 98%) as a white solid, as a mixture of isomers in ratio (2.8 :1). The derived ester (6.0 g, 10 mmol) in THF (20 mL) was gradually added to a stirred suspension of lithium aluminium hydride (0.77 g, 20 mmol) in THF (50 mL) at 0 °C. The mixture was heated at reflux at 100 °C for 2 h, then worked up and purified as before to give (*E*/*Z*)-13-((1*R*,2*S*)-*cis*-2-eicoscylcyclopropyl)-tridec-12-en-1-ol (5.0 g, 91%) as a white solid. Hydrazine monohydrate (20 mL), acetic acid (2 mL), and sat. aq. copper sulfate (2 mL) were added in succession to the derived alcohols (5.0 g, 9.7 mmol) in isopropanol (250 mL) at 80 °C, and then sodium metaperiodate solution (20 g, 97 mmol) in hot water (60 mL) was carefully added dropwise, maintaining the temperature at 80 °C, then worked up as above. The product was recrystallised from chloroform to give the title compound **8**.

Yield: 3.8 g (75%); mp 72–74 °C; $[\alpha]_D^{26}$ –0.33 (*c* 2.03, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$): δ = 3.65 (t, *J* = 6.6 Hz, 2 H), 1.58 (pent, *J* = 6.65 Hz, 4 H), 1.40–1.22 (m, 57 H), 1.15–1.10 (m, 2 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.65 (m, 2 H), 0.56 (dt, *J* = 4.0, 7.8 Hz, 1 H), –0.32 (q, *J* = 5.35 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): 63.1, 32.8, 32.0, 30.2, 29.7, 29.63, 29.6, 29.4, 29.3, 28.7, 25.7, 22.7, 15.8, 14.1, 10.9.

IR: 3383, 2917, 2848, 1465, 1064, 723, 449, 426, 417, 412 cm^{-1}.

13-((1*R*,2*S*)-2-Eicosylcyclopropyl)tridecanal (9)

Alcohol **8** (4.5 g, 8.6 mmol) in dichloromethane (80 mL) was added to a stirred suspension of PCC (4.66 g, 22.0 mmol, 2.5 mol equiv) in dichloromethane (60 mL) in portions at r.t. The mixture was stirred for 2 h and then diluted with petrol/ether 2:1 (300 mL), filtered through a pad of Celite on silica, then washed well with warm ether (400 mL) and the filtrate was evaporated to give a residue. This was purified by column chromatography on silica eluting with petrol/ether 2:1 to give the title compound **9**.

Yield: 3.6 g (84%); mp 61–64 °C, $[\alpha]_D^{22}$ +1.6 (*c* 1.2, $CHCl_3$) (enantiomer –1.7 (*c* 1.2, $CHCl_3$)).[28]

^1H NMR (500 MHz, $CDCl_3$): 9.77 (t, *J* = 1.9 Hz, 1 H), 2.42 (br td, *J* = 1.9, 7.3 Hz, 2 H), 1.63 (pent, *J* = 6.9 Hz, 2 H), 1.38–1.12 (br m, 56 H), 1.15–1.1 (m, 2 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 0.67–0.61 (m, 2 H), 0.56 (td, *J* = 3.7, 7.8 Hz, 1 H), –0.32 (br q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): 203.0, 43.9, 31.9, 30.2, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 22.6, 22.0, 15.7, 14.1, 10.8.

IR: 2991, 2848, 1715, 1469, 1391, 1018, 720 cm^{-1}.

5-[13-((1*R*,2*S*)-*cis*-2-Eicosylcyclopropyl)tridec-ane-1-sulfonyl]-phenyl-1*H*-tetrazole (10)

(a) 13-((1*R*,2*S*)-*cis*-2-Eicosylcyclopropyl)tridecan-1-ol **8** (4.0 g, 7.7 mmol) was dissolved in anhydrous THF (10 mL) together with triphenylphosphine (2.6 g, 10 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (1.8 g, 10 mmol). The mixture was cooled to 0 °C, followed by the addition of DEAD (1.7 mL, 10 mmol) in anhydrous THF (5 mL). The mixture was stirred overnight at r.t., evaporated, then the residue was washed with petrol/ether (10:1) and then filtered. The filtrate was evaporated and the product was purified by column chromatography eluting with chloroform to give 5-[13-((1*R*,2*S*)-*cis*-2-eicosylcyclopropyl)tridecyl-sulfanyl]phenyl-1*H*-tetrazole.

Yield: 5.1 g (97%); mp 42–44 °C; $[\alpha]_D^{22}$ –1.2 (*c* 1.3, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{43}H_{76}N_4SNa$: 703.5683; found: 703.5658.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.62–7.52 (m, 5 H), 3.42 (t, *J* = 7.4 Hz, 2 H), 1.84 (pent, *J* = 7.5 Hz, 2 H), 1.47 (pent, *J* = 7.3 Hz, 2 H), 1.43–1.12 (m, 58 H), 0.91 (t, *J* = 6.9 Hz, 3 H), 0.71–0.64 (m, 2 H), 0.59 (dt, *J* = 4.1, 8.3 Hz, 1 H), –0.35 (q, *J* = 4.9 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.8, 134.2, 133.3, 130.1, 125.9, 33.7, 30.2, 29.7, 29.65, 29.6, 29.5, 29.43, 29.4, 29.1, 29.0, 28.73, 28.7, 22.9, 15.6, 14.4, 11.1.

IR: 1600, 1465, 1378, 1244, 1168, 1015, 693 cm^{-1}.

(b) Sodium hydrogen carbonate (1.7 g, 20 mmol) was added to a stirred solution of the above tetrazole (3.0 g, 4.4 mmol) in dichloromethane (50 mL), followed by the addition of a mixture of anhydrous 3-chloroperoxybenzoic acid (2.0 g, 88 mmol) and dichloromethane (50 mL). The reaction was stirred at r.t. for 18 h to give an off-white precipitate, then aq. sodium hydroxide (5%; 100 mL) was added and the mixture was stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with water (2 × 200 mL), dried and evaporated. The product was recrystallised from methanol/acetone (1:1), which gave a white solid of the title compound **10**.

Yield: 2.1 g (67%); mp 50–52 °C; $[\alpha]_D^{22}$ +1.7 (*c* 1.4, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{43}H_{76}N_4O_2SNa$: 735.5581; found: 735.5596.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 5 H), 3.74 (distorted t, *J* = 8.0 Hz, 2 H), 1.96 (br pent, *J* = 7.8 Hz, 2 H), 1.50 (br pent, *J* = 7.4 Hz, 2 H), 1.45–1.10 (m, 58 H), 0.89 (t, *J* = 6.8 Hz, 3 H), 0.66–0.64 (m, 2 H), 0.57 (dt, *J* = 4.1, 8.5 Hz, 1 H), –0.33 (q, *J* = 4.8 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 134.0, 133.4, 130.6, 126.1, 56.4, 31.9, 30.3, 29.7, 29.5, 29.48, 29.4, 29.2, 28.9, 28.7, 28.2, 22.8, 22.2, 16.1, 14.3, 11.0.

IR: 1764, 1597, 1464, 1377, 1357, 1218, 1147, 1013, 685, 633 cm^{-1}.

((1*R*,2*S*)-2-(14-((1*R*,2*S*)-2-Eicosylcyclopropyl)tetradecyl)cyclopropyl)methanol (12)

(a) LiHMDS (12.8 mL, 13 mmol, 1.06 M, 1.5 mol) was added dropwise with stirring to aldehyde **9** (3.6 g, 6.9 mmol) and sulfone **11** (3.3 g, 7.5 mmol)[32,33] in anhydrous THF (30 mL) under nitrogen at–10 to –4 °C. The mixture was allowed to reach r.t., stirred for 5 h, then the reaction was quenched with sat. aq. ammonium chloride (50 mL) and petrol/ether 1:1 (100 mL). The organic layer was separated and the aqueous layer was re-extracted with petrol/ether 1:1 (2 × 100 mL). The combined organic layers were dried and evaporated to give a solid; column chromatography on silica eluting with petrol/ether 10:1 gave a mixture of alkenes (3.0 g, 65 %).

(b) $LiAlH_4$ (0.2 g) was added to stirred THF (100 mL) at 0 °C under nitrogen to ensure THF dryness. Then further $LiAlH_4$ (1.0 g, 26 mmol) was added. A solution of alkenes (3.0 g, 4.5 mmol) in anhydrous THF (20 mL) was added dropwise by using a syringe at 0 °C and the mixture was heated at reflux for 3 h, then cooled to 0 °C and the reaction was quenched with sat. aq. sodium sulphate decahydrate (20 mL), which was added dropwise and stirred at r.t until a white precipitate was formed followed by addition of $MgSO_4$ (20 g). THF (40 mL) was added and the mixture was filtered through a pad of silica, dried and the solvent evaporated to give a mixture of alcohols (2.4 g, 89%), which was used for the next step without further purification.

(c) Sodium (meta)periodate (20.3 g, 95.0 mmol) in hot water (50 mL) was added over 70 min at 70–80 °C to a stirred solution of above alcohol (2.9 g, 4.8 mmol) in isopropyl alcohol (250 mL), acetic acid (1.5 mL), sat. aq. copper sulphate (1.5 mL) and hydrazine hydrate (20 mL). The mixture was stirred for 2 h until it reached r.t., then diluted with water (100 mL) and petrol/ether 5:1 (400 mL). Due to the low solubility of the product, the mixture was warmed (40 °C) to allow separation. The aqueous layer was re-extracted with warm petrol/ether 5:1 (3 × 100 mL). The combined organic layers were dried and evaporated to give a solid. Column chromatography on silica eluting with petrol/ether 5:1 gave the title compound **12**.

Yield: 1.8 g (63%); white solid; mp 72–74 °C; $[\alpha]_D^{26}$ +8.3 (*c* 0.86, $CHCl_3$)

MS: *m*/*z* $[M + H]^+$ calcd for $C_{41}H_{81}O$: 590.0978; found: 590.0980.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.66 (dd, *J* = 7.3, 11 Hz, 1 H), 3.59 (dd, *J* = 7.9, 11 Hz, 1 H), 1.56 (br m, 4 H), 1.47–1.20 (br m, 60 H), 1.17–1.05 (m, 4 H), 0.9–0.84 (including t at δ 0.88 with *J* = 6.95 Hz, 4 H), 0.70 (dt, *J* = 4.4, 8.2 Hz, 1 H), 0.68–0.63 (m, 2 H), 0.57 (dt, *J* = 4.1, 8.5 Hz, 1 H), –0.03 (q, *J* = 5.35 Hz, 1 H), –0.32 (q, *J* = 5.35 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 63.4, 31.9, 30.2, 30.18, 29.7, 29.65, 29.6, 29.4, 28.7, 28.6, 22.7, 18.2, 16.2, 15.8, 14.1, 10.9, 9.5.

IR: 3375, 2852, 1771, 1464, 1370, 1170, 1064, 1037, 964, 932, 823 cm^{-1}.

(1*S*,2*R*)-2-[14-((1*R*,2*S*)-2-Eicosylcyclopropyl)tetradecyl]cyclopropyl Methanol (14)

LiHMDS (3.7 mL, 4.0 mmol) was added to a stirred solution of butyric acid (1*S*,2*R*)-(*cis*-2-formylcyclopropyl)methyl ester **13** (0.5 g 3.0 mmol) and sulfone **10** (2.1 g, 30 mmol) in anhydrous THF (30 mL) at –10 °C. The mixture was allowed to reach r.t. and stirring was continued for 1.5 h, then worked up and purified as before to give butyric acid (1*S*,2*R*)-2-[(*E*/*Z*)-14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradec-1-enyl]cyclopropylmethyl ester (1.2 g, 62%) as a white solid as a mixture in ratio 2.5:1. The above ester (1.2 g, 1.8 mmol) in THF (10 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (0.14 g, 3.7 mmol) in THF (10 mL) at –10 °C under nitrogen atmosphere. The reaction was heated at reflux at 100 °C for 2.5 h then worked up as before to give (1*S*,2*R*)-2-[(*E*/*Z*)-14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradec-1-enyl]cyclopropyl methanol (0.77 g, 72 %) as a white solid. Hydrazine monohydrate (7 mL), acetic acid (1 mL), and sat. aq. copper sulfate (1 mL) were added in succession at 70–80 °C to a stirred solution of the above alcohol (0.77 g, 1.3 mmol) in isopropyl alcohol (50 mL). Still maintaining the temperature at 80 °C, a solution of sodium metaperiodate (2.8 g, 13 mmol) in hot water (10 mL) was carefully added dropwise. The mixture was allowed to reach r.t. and stirred for 1 h, then worked up as above to give the title compound **14**.

Yield: 0.55 g (71%); white solid; mp 51–53 °C; $[\alpha]_D^{21}$ –7.3 (*c* 1.0, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{41}H_{80}ONa$: 611.6; found: 611.5.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.7 (dd, *J* = 7.3, 11.4 Hz, 1 H), 3.59 (dd, *J* = 8.0, 11.4 Hz, 1 H), 1.62–1.55 (m, 4 H), 1.45–1.2 (m, 60 H), 1.15–1.05 (m, 4 H), 1.15–1.05 (m, 4 H), 0.92–0.83 (including t at δ 0.89 with *J* = 6.8 Hz, 4 H), 0.72 (dt, *J* = 4.3, 8.3 Hz, 1 H), 0.69–0.63 (m, 2 H), 0.57 (dt, *J* = 4.1, 8.5 Hz, 1 H), –0.03 (q, *J* = 5.3 Hz, 1 H), –0.33 (q, *J* = 5.0 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 63.6, 32.2, 31.9, 30.2, 29.7 (very br), 29.4, 28.7, 22.9, 18.4, 16.2, 15.8, 14.2, 10.9, 9.47.

IR: 3368, 2852, 1771, 1464, 1370, 1170, 1064, 1037, 964, 932, 823 cm^{-1}.

(1*R*,2*S*)-2-[14-((1*S*,2*R*)-2-Eicosylcyclopropyl)tetradecyl]cyclopropyl Methanol (16)

LiHMDS (6.1 mL, 6.5 mmol) was added to a stirred solution of aldehyde **5** (0.85 g, 5.0 mmol) and sulfone **15** (3.6 g, 5.0 mmol) (see the Supporting Information) in anhydrous THF (50 mL) at –10 °C. The reaction mixture was worked up as before to give butyric acid (1*R*,2*S*)-2-[(*E*/*Z*)-14-((1*S*,2*R*)-2-eicosylcyclopropyl)tetradec-1-enyl]cyclopropylmethyl ester (2.5 g, 78%) as a white solid. Lithium aluminium hydride (0.29 g, 7.62 mmol) in THF (20 mL) was reacted with the ester (2.5 g, 3.8 mmol) in THF (20 mL). Work up as before gave (1*R*,2*S*)-2-[(*E*/*Z*)-14-((1*S*,2*R*)-2-eicosylcyclopropyl)tetradec-1-enyl]cyclopropylmethanol (1.1 g, 50%). Hydrazine monohydrate (10 mL), acetic acid (1 mL) and sat. aq. copper sulfate (1 mL) were added in succession to the unsaturated alcohols (1.1 g, 1.9 mmol) in isopropanol (30 mL), and the mixture was treated with sodium metaperiodate (4.0 g, 18.8 mmol) in hot water (10 mL) at 80 °C. The reaction was worked up as before and the product was extracted with petrol/ether (1:1, 3 × 50 mL), then recrystallised from petrol to give a (1*R*,2*S*)-2-[14-((1*S*,2*R*)-2-eicosylcyclopropyl)tetradecyl]cyclopropylmethanol **16**.

Yield: 0.7 g (63%); white solid; mp 59–61 °C; $[\alpha]_D^{21}$ +7.6 (*c* 1.2, $CHCl_3$).

MALDI MS: *m*/*z* $[M + Na]^+$ calcd for $C_{41}H_{80}ONa$: 611.6; found: 611.9.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.7 (dd, *J* = 7.5, 11.5 Hz, 1 H), 3.59 (dd, *J* = 8.0, 11.5 Hz, 1 H), 1.62–1.55 (m, 4 H), 1.45–1.2 (m, 60 H), 1.15–1.05 (m, 4 H), 0.92–0.83 (including t at δ 0.89 with *J* = 6.8 Hz, 4 H), 0.73 (dt, *J* = 4.5, 8.4 Hz, 1 H), 0.68–0.63 (m, 2 H), 0.58 (dt, *J* = 4.1, 8.5 Hz, 1 H), –0.03 (q, *J* = 5.5 Hz, 1 H), –0.33 (q, *J* = 5.0 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 63.8, 32.4, 31.9, 30.2, 29.7 (very broad), 29.4, 28.7, 22.9, 18.6, 16.2, 15.8, 14.2, 10.9, 9.47.

IR: 3365, 2850, 1770, 1462, 1370, 1169, 1062, 1035, 963, 930, 821 cm^{-1}.

5-(((1*R*,2*S*)-2-(14-((1*R*,2*S*)-2-Eicosylcyclopropyl)tetradecyl)cyclopropyl)methylsulfonyl)-1-phenyl-1*H*-tetrazole (17)

(a) Alcohol **12** (1.7 g, 2.9 mmol) was dissolved in anhydrous THF (50 mL) together with triphenylphosphine (1.14 g, 4.3 mmol, 1.5 equiv) and 1-phenyl-1*H*-tetrazole-5-thiol (0.82 g, 4.6 mmol, 1.6 equiv). The mixture was cooled to 0 °C, followed by the addition of DEAD (0.82 g, 4.0 mmol, 1.4 equiv) in anhydrous THF (5 mL). The mixture was stirred at r.t. overnight. The solvent was evaporated to a small volume to which petrol/ether 1:1 (100 mL) was added and the mixture was stirred at r.t. for 45 min, then filtered. The filtrate was dried and evaporated to give a solid. Column chromatography on silica eluting with petrol/ether 10:2 gave 5-[(1*R*,2*S*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropylmethyl-sulfanyl]-1-phenyl-1*H*-tetrazole.

Yield: 2.0 g (93%); $[\alpha]_D^{26}$ +3.2 (*c* 1.3, $CHCl_3$).

MALDI MS: *m*/*z* $[M + Na]^+$ calcd for $C_{48}H_{84}N_4SNa$: 771.6; found: 771.5.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65–7.5 (m, 5 H), 3.49 (d, *J* = 7.9 Hz, 2 H), 1.56 (br s, 3 H), 1.49 (m, 1 H), 1.38–1.13 (br m, 63 H), 0.95–0.9 (m, 1 H), 0.88 (t, *J* = 7.3 Hz, 3 H), 0.83 (dt, *J* = 5.1, 8.5 Hz, 1 H), 0.67–0.62 (m, 2 H), 0.56 (dt, *J* = 4.1, 8.2 Hz, 1 H), 0.08 (q, *J* = 5.4 Hz, 1 H), –0.32 (q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.6, 133.8, 132.1, 130.0, 129.7, 128.5, 128.4, 128.4, 123.8, 35.0, 31.9, 30.2, 30.0, 29.7, 29.65, 29.5, 28.7, 28.5, 22.7, 18.0, 15.8, 14.6, 14.1, 12.5, 10.9.

IR: 3068, 2988, 2916, 2849, 1599, 1502, 1469, 1381, 1234, 1016, 824, 754, 694, 542, 458, 451, 435 cm^{-1} .

(b) Sodium hydrogen carbonate (1.03 g, 12 mmol, 4.5 equiv) was added to a stirred solution of the above tetrazole (2.0 g, 2.7 mmol) in dichloromethane (100 mL), followed by the addition of a mixture of anhydrous 3-chloroperoxybenzoic acid 70% (1.67 g, 9.7 mmol, 2.5 equiv) in CH_2Cl_2 (50 mL). The reaction was stirred at r.t. for 48 h to give an off-white precipitate. Aq. sodium hydroxide (5%, 80 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 200 mL). The combined organic layers were washed with water (2 × 200 mL), dried and evaporated. The product was recrystallised from methanol/acetone (1:1), to give the title compound **17**.

Yield: 1.77 g (85%); $[\alpha]_D^{20}$ –18 (*c* 1.5, $CHCl_3$).

MS: *m*/*z* $[M + H]^+$ calcd for $C_{48}H_{85}N_4O_2S$: 782.2976; found: 782.2980.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2 H), 7.65–7.58 (m, 3 H), 3.98 (dd, *J* = 5.35, 14.5 Hz, 1 H), 3.57 (dd, *J* = 9.15, 14.5 Hz, 1 H), 1.5–1.2 (m, 66 H), 1.17–1.1 (m, 1 H), 1.03–0.94 (m, 1 H), 0.90–0.86 (including t at δ 0.89 with *J* = 6.95 Hz, 4 H), 0.68–0.64 (m, 2 H), 0.56 (dt, *J* = 4.1, 8.2 Hz, 1 H), 0.25 (q, *J* = 5.7 Hz, 1 H), –0.32 (q, *J* = 5.35 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.7, 133.1, 131.4, 129.7, 125.2, 57.1, 31.9, 30.2, 29.64, 29.6, 29.44, 29.4, 29.1, 28.7, 22.7, 15.9, 15.8, 14.1, 11.4, 10.9, 8.0.

IR: 2990, 2916, 2849, 1498, 1470, 1340, 1152, 761, 718, 687 cm^{-1}.

5-[(1*S*,2*R*)-2-[14-((1*R*,2*S*)-2-Eicosylcyclopropyl)tetradecyl]cyclopropylmethanesulfonyl]-1-phenyl-1*H*-tetrazole (18)

(a) Alcohol **14** (0.55 g, 0.85 mmol) was dissolved in anhydrous THF (5 mL) and then triphenylphosphine (0.30 g, 1.1 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (0.2 g, 1.1 mmol) were added. The mixture was cooled to 0 °C and treated as above with DEAD (0.18 mL, 1.1 mmol) in anhydrous THF (5 mL). After stirring at r.t. overnight, the reaction mixture was worked up as above. Column chromatography eluting with dichloromethane gave 5-[(1*S*,2*R*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropylmethyl-sulfanyl]-1-phenyl-1*H*-tetrazole.

Yield: 0.7 g (92 %); mp 43–50 °C; $[\alpha]_D^{20}$ –2.1 (*c* 1.7, $CHCl_3$).

MALDI MS: *m*/*z* $[M + Na]^+$ calcd for $C_{48}H_{84}N_4SNa$: 771.6; found: 771.4.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.55 (m, 5 H), 3.49 (d, *J* = 7.9 Hz, 2 H), 1.60–1.11 (including m at 1.47–1.53 for one cyclopropane proton, 67 H), 0.95–0.9 (m, 1 H), 0.89 (t, *J* = 6.9 Hz, 3 H), 0.84 (dt, 4.7, 1 H, 8.2 Hz), 0.67–0.63 (m, 2 H), 0.57 (dt, *J* = 3.4, 8.2 Hz, 1 H), 0.08 (q, *J* = 5.4 Hz, 1 H), –0.32 (q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 133.8, 130, 123.8, 35.0, 31.9, 30.9, 29.5, 28.5, 22.7, 21.0, 18.0, 15.8, 14.6, 14.1, 12.

IR: 3059, 2923, 1463, 1340, 1275, 1169, 1088 cm^{-1}.

(b) Ammonium molybdate(VI) tetrahydrate (2.90 g, 2.34 mmol) was dissolved in cold hydrogen peroxide (35% w/w, 10 mL) and was added gradually to a stirred solution of the above tetrazole (0.35 g, 0.47 mmol) in IMS/THF (30:10 mL) at 5–10 °C, then allowed to attain r.t. and stirred for another 2 h after which further ammonium

molybdate(VI) tetrahydrate (1.20 g, 0.94 mmol) in cold hydrogen peroxide (5 mL) was added. The reaction was stirred for 18 h and then poured into water (200 mL) and extracted with dichloromethane (3 × 50 mL). The organic layers were washed with water (2 × 50 mL) and concentrated. Column chromatography eluting with petrol/ether (5:2) gave the title compound **18**.

Yield: 0.15 g (41%); mp 68–69 °C; $[\alpha]_D^{20}$ +17 (*c* 1.2, $CHCl_3$).

MS MALDI: *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{84}O_2N_4SNa$: 803.6; found: 803.5.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2 H), 7.65–7.58 (m, 3 H), 3.98 (dd, *J* = 5.7, 14.9 Hz, 1 H), 3.57 (dd, *J* = 9.5, 14.9 Hz, 1 H), 1.38–1.13 (m, 68 H), 1.05–0.97 (m, 1 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.67–0.63 (m, 2 H), 0.57 (dt, *J* = 4.1, 8.2 Hz, 1 H), 0.08 (q, *J* = 5.6 Hz, 1 H), –0.33 (, *J* = 5.0 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 131.4, 129.7, 125.2, 57.1, 31.9, 30.2, 29.7, 29.5, 29.1, 28.7, 22.7, 15.9, 14.1, 11.4, 10.9, 8.0.

IR: 2923, 2854, 1462, 1377, 1338, 1156 cm^{-1}.

5-[(1*R*,2*S*)-2-[14-((1*S*,2*R*)-2-Eicosylcyclopropyl)tetradecyl]cyclopropylmethanesulfonyl]-1-phenyl-1*H*-tetrazole (19)

(a) Alcohol **16** (0.70 g, 1.2 mmol) was dissolved in anhydrous THF (5 mL) together with triphenylphosphine (0.41 g) and 1-phenyl-1*H*-tetrazole-5-thiol (0.28 g, 1.55 mmol). The mixture was cooled to 0 °C, followed by the addition of DEAD (0.24 mL, 1.55 mmol) in anhydrous THF (5 mL), and then stirred overnight at r.t. Work up as above followed by column chromatography eluting with dichloromethane gave the sulfane.

Yield: 0.8 g (89%); mp 43–50 °C; $[\alpha]_D^{20}$ +1.5 (*c* 1.4, $CHCl_3$).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{84}N_4SNa$: 771.6314; found: 771.6308.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62–7.54 (m, 5 H), 3.50 (d, *J* = 8.0 Hz, 2 H), 1.60–1.10 (including m at 1.46–1.51 for one cyclopropane proton, 67 H), 0.92–0.97 (m, 1 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.83 (dt, 4.7, 8.1 Hz, 1 H), 0.68–0.63 (m, 2 H), 0.57 (dt, *J* = 3.8, 7.9 Hz, 1 H), 0.23 (q, *J* = 5.4 Hz, 1 H), –0.33 (q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 133.8, 129.9, 123.8, 35.0, 31.9, 30.1, 29.5, 28.7, 22.7, 17.9, 15.8, 14.6, 14.1, 12.5, 10.9.

IR: 3059, 2920, 1463, 1339, 1275, 1169, 1088, 1018 cm^{-1}.

(b) Ammonium molybdate(VI) tetrahydrate (5.0 g, 4.0 mmol) was dissolved in cold hydrogen peroxide (35%,w/w, 10 mL), and added gradually to a stirred mixture of the above sulfane (0.60 g, 0.80 mmol) in IMS/THF (30:10 mL) at 5–10 °C. The reaction was stirred at r.t. for 2 h, then more ammonium molybdate(VI) tetrahydrate (2.0 g, 1.6 mmol) in cold hydrogen peroxide (5 mL) was added. The reaction was stirred for 18 h and then poured into water (200 mL) and extracted with dichloromethane (3 × 50 mL). The organic layers were washed with more water (2 × 50 mL), dried and concentrated. Column chromatography eluting with petrol/ether (5:2) gave **19**.

Yield: 0.2 g (46%); whitish solid; mp 65–66 °C; $[\alpha]_D^{20}$ –18 (*c* 1.4, $CHCl_3$).

MALDI MS: *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{84}O_2N_4SNa$: 803.6; found: 803.4.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72–7.68 (m, 2 H), 7.65–7.58 (m, 3 H), 3.98 (dd, *J* = 5.7, 14.9 Hz, 1 H), 3.57 (dd, *J* = 9.2, 14.9 Hz, 1 H), 1.38–1.18 (m, 68 H), 1.05–0.97 (m, 1 H), 0.89 (t, *J* = 6.7 Hz, 3 H), 0.67–0.63 (m, 2 H), 0.57 (dt, *J* = 4.1, 8.2 Hz, 1 H), 0.08 (q, *J* = 5.6 Hz, 1 H), –0.33 (q, *J* = 5.0 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 131.4, 129.7, 125.2, 57.1, 31.9, 30.2, 29.7, 29.5, 29.1, 28.7, 22.7, 15.9, 14.1, 11.4, 10.9, 8.0.

IR: 2922, 2852, 1464, 1377, 1339, 1156 cm^{-1}.

(*R*)-2-((*R*)-1-(*tert*-Butyldimethylsilanyloxy)-12-{(1*R*,2*S*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl}dodecyl)hexacosanoic Acid Methyl Ester (21)

(a) LiHMDS (2.78 mL, 2.9 mmol, 1.3 mol equiv, 1.06 M) was added to a stirred solution of sulfone **17** (1.77 g, 2.27 mmol) and aldehyde **20** (1.77 g, 2.5 mmol, 1.1 mol equiv) in anhydrous THF (40 mL) at –10 °C under nitrogen. The solution was allowed to reach r.t., stirred for 2 h, then petrol/ether 10:1 (100 mL) and sat. aq. NH_4Cl (50 mL) were added. The organic layer was separated and the aqueous layer was re-extracted with petrol/ether 10:1 (2 × 100 mL). The combined organic layers were dried and evaporated. Column chromatography eluting with petrol/ether 20:1 gave the product alkenes (2.5 g, 87%) as an *E*/*Z*-mixture in ratio 2.5:1.

(b) Dipotassium azodicarboxylate (3.0 g, 0.015 mol) was added to a stirred solution of the above alkenes (2.4 g, 1.9 mmol) in anhydrous THF (20 mL) and MeOH (25 mL) and then cooled to 0 °C. Then acetic acid (5 mL) in THF (5 mL) was added dropwise at a rate of 1 mL/15 min. The reaction turned bright-yellow and was left stirring for 9 h at 5 °C. The procedure was repeated as above with further dipotassium azodicarboxylate, acetic acid, stirring for a further 9 h, then quenched by adding the mixture in small portions to sat. aq. $NaHCO_3$ (50 mL). After extraction, column chromatography eluting with petrol/ether 20:1 gave the title compound **21**.

Yield: 2.07 g (86%); $[\alpha]_D^{28}$ +3.8 (*c* 1.40, $CHCl_3$).

MALDI MS: *m*/*z* [M + Na]$^+$ calcd for $C_{85}H_{168}O_3SiNa$: 1288.3; found: 1288.4.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95–3.88 (m, 1 H), 3.7 (s, 3 H), 2.54 (ddd, *J* = 2.9, 6.4, 9.2 Hz, 1 H), 1.58–1.10 (m, 134 H), 0.87 (t *J* = 6.7 Hz, 6 H), 0.86 (s, 9 H), 0.68–0.62 (m, 4 H), 0.58 (dt, *J* = 3.8, 7.9 Hz, 2 H), 0.05 (s, 3 H), 0.03 (s, 3 H), –0.32 (q, *J* = 4.75 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.1, 73.2, 51.6, 51.2, 41.4, 36.1, 33.74, 33.7, 32.0, 30.3, 29.9, 29.74, 29.7, 29.65, 29.6, 29.5, 29.4, 28.9, 28.8, 27.9, 27.7, 27.5, 25.8, 23.7, 22.7, 22.6, 20.5, 19.4, 18.0, 15.8, 14.1, 10.9, –4.4, –4.9.

IR: 2923, 2853, 1742, 1465, 1253 cm^{-1}.

(*R*)-2-((*R*)-1-Hydroxy-12-{(1*R*,2*S*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl}dodecyl)hexacosanoic Acid (22)

(a) A dry polyethylene vial equipped with an acid-resistant rubber septum was charged with the above TBDMS methyl ester (1.9 g, 1.5 mmol) and anhydrous pyridine (2 mL) in anhydrous THF (25 mL) and stirred at r.t. under argon. To it was added hydrogen fluoride-pyridine complex as ca. 70% hydrogen fluoride (3 mL) at 5 °C. The mixture was then stirred at 45 °C for 17 h. The mixture was diluted with petrol/ether 10:1 (100 mL) and neutralised by pouring it slowly into sat. aq. sodium bicarbonate until no more CO_2 was liberated. The product was extracted with warm petrol/ether 10:1 (2 × 100 mL), and the combined organic layers were washed with brine (100 mL). The organic layer was dried and evaporated to give a residue, which was purified by chromatography eluting with petrol/ether 10:1 to give methyl (*R*)-2-((*R*)-1-hydroxy-12-{(1*R*,2*S*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl}dodecyl)hexacosanoate.

Yield: 1.32 g (76%); $[\alpha]_D^{32}$ +4.3 (*c* 0.94, $CHCl_3$).

MALDI MS: *m*/*z* [M + Na]$^+$ calcd for $C_{79}H_{154}O_3Na$: 1175.0; found: 1174.9.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.68–3.62 (m, 1 H), 2.44 (dt, *J* = 5.4, 9.5 Hz, 1 H), 1.72–1.14 (m, 135 H), 0.88 (t, 6 H, *J* = 6.95 Hz), 0.68–0.62 (m, 4 H), 0.57 (dt, *J* = 4.1, 8.6 Hz, 2 H), –0.32 (q, *J* = 4.8 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.2, 72.3, 51.5, 50.9, 35.7, 31.9, 30.2, 29.7, 29.66, 29.63, 29.6, 29.56, 29.55, 29.5, 29.42, 29.4, 28.7, 27.4, 25.7, 22.7, 15.8, 14.1, 10.9.

IR: 3400, 3016, 2905, 2858, 1463, 1199, 669 cm^{-1}.

(b) The above methyl ester (1.0 g, 0.9 mmol) was dissolved in THF (15 mL), MeOH (1 mL) and water (1.5 mL), and then lithium hydroxide monohydrate (1.10 g, 26.2 mmol, 30 equiv) was added to the stirred mixture at r.t. The reaction was heated at 45 °C for 18 h, then cooled to r.t. and diluted with petrol/EtOAc (7:2, 100 mL), followed by the dropwise addition of sat. aq. potassium hydrogen sulfate (20 mL), which brought the mixture to pH 1. The aqueous layer was separated and re-extracted with warm petrol/EtOAc (7:2, 3 × 100 mL). The combined organic layers were dried and concentrated to give a crude product, which was purified by column chromatography, eluting with warm petrol/EtOAc (7:2) to give compound **22**.

Yield: 0.92 g (93%); R_f 0.42 (above solvent); $[\alpha]_D^{24}$ +2.0 (*c* 1.2, $CHCl_3$).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{78}H_{152}O_3Na$: 1161.06; found: 1160.59.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75–3.70 (m, 1 H), 2.44 (dt, *J* = 5.1, 8.8 Hz, 1 H), 1.74–1.14 (m, 136 H), 0.88 (t, *J* = 7.0 Hz, 6 H), 0.68–0.62 (m, 4 H), 0.57 (dt, *J* = 4.1, 8.6 Hz, 2 H), –0.32 (q, *J* = 5.1 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 182.1, 72.2, 50.8, 35.5, 31.9, 30.2, 29.7, 29.66, 29.6, 29.55, 29.42, 29.4, 28.7, 27.3, 25.7, 22.7, 15.8, 14.1, 10.9.

IR: 3427, 3019, 2916, 2848, 1467, 1215, 759, 669 cm^{-1}.

(*R*)-2-((*R*)-1-Hydroxy-12-[(1*S*,2*R*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl]dodecyl)hexacosanoic Acid (23)

(a) LiHMDS (0.30 mL, 0.24 mmol) was added to a stirred solution of aldehyde **20** (0.12 g, 0.17 mmol) and tetrazole **18** (0.15 g, 0.19 mmol) in anhydrous THF (5 mL) at –10 °C under nitrogen, then stirred for 1.5 h at r.t. Water (10 mL) was added and the mixture was extracted with petrol/ether (1:1, 3 × 10 mL) and the combined organic layers were washed with brine (2 × 10 mL), dried and filtered. The filtrate was concentrated and the residue purified by column chromatography, eluting with petrol/EtOAc (20:1), to give (*R*)-2-((*E*/*Z*)-(*R*)-1-(*tert*-butyldimethylsilanyloxy)-12-[(1*S*,2*R*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl]dodec-11-enyl)hexacosanoic acid methyl ester (0.12 g, 49%).

(b) Dipotassium azodicarboxylate (2.0 g, 10 mmol) was added to a stirred solution of the derived esters (0.11 g, 0.09 mmol) in anhydrous THF (3 mL) and MeOH (1.5 mL) and then cooled to 0 °C under nitrogen. Glacial acetic acid (0.5 mL) was dissolved in THF (1.0 mL), and then added dropwise to the reaction mixture, which was stirred overnight at r.t. The process was repeated using the same amount of glacial acetic acid in THF until there was a change in colour from bright yellow to off-white. Work up as above gave a very thick oil of the corresponding TBDMS methyl ester.

Yield: 0.1 g (90%).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{85}H_{168}O_3SiNa$: 1288.3; found: 1288.6.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89 (td, *J* = 4.8, 6.6 Hz, 1 H), 3.64 (s, 3 H), 2.51 (ddd, *J* = 3.8, 7.2, 11.1 Hz, 1 H), 1.55–1.24 (m, 134 H), 0.85 (t, *J* = 7.0 Hz, 6 H), 0.84 (s, 9 H), 0.65–0.62 (m, 4 H), 0.55 (dt, *J* = 3.5, 7.9 Hz, 2 H), 0.05 (, 3 H), 0.02 (s, 3 H),–0.35 (q, *J* = 5.0 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.1, 73.2, 51.4, 33.7, 31.9, 30.2, 29.8, 29.7, 29.67, 29.62, 29.5, 29.45, 29.4, 28.7, 27.4, 25.8, 23.7, 22.7, 18.0, 15.8, 14.1, 10.9, –4.3, –4.9.

IR: 2923, 2853, 1742, 1464, 1254 cm^{-1}.

(c) A dry polyethylene vial equipped with an acid-resistant rubber septum was charged with the above TBDMS methyl ester (0.10 g, 0.08 mmol) and anhydrous pyridine (0.1 mL) in anhydrous THF (4 mL) and stirred at r.t. under nitrogen. To it was added hydrogen fluoride-pyridine complex as ca. 70% hydrogen fluoride (0.7 mL) at 5 °C. The mixture was stirred at 45 °C for 17 h, then worked up and purified as above to give (*R*)-2-((*R*)-1-hydroxy-12-[(1*S*,2*R*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl]dodecyl)hexacosanoic acid methyl ester.

Yield: 0.03 g (33%); white solid; mp 55–57 °C; $[\alpha]_D^{19}$ +2.5 (*c* 1.7, $CHCl_3$).

MALDI MS: *m*/*z* [M + Na]$^+$ calcd for $C_{79}H_{154}O_3Na$: 1174.2; found: 1174.4.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.68–3.62 (m, 1 H), 2.46–2.42 (m, 1 H), 1.74–1.70 (m, 1 H), 1.61–1.57 (m, 2 H), 1.48–1.15 (m, 132 H,), 0.89 (t, *J* = 6.6 Hz, 6 H), 0.68–0.62 (m, 4 H), 0.55 (dt, *J* = 4.1, 8.2 Hz, 2 H), –0.33 (q, *J* = 4.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.2, 72.3, 51.2, 35.7, 31.9, 30.2, 29.7, 29.65, 29.6, 29.5, 29.4, 29.36, 28.7, 27.4, 25.7, 22.7, 15.8, 14.1, 10.9.

IR: 3520, 2924, 2855, 2367, 1712, 1461, 1377, 1165, 721 cm^{-1}.

(d) The above methyl ester (0.030 g, 0.026 mmol) was dissolved in THF (4.0 mL), MeOH (0.5 mL) and water (0.7 mL), and then lithium hydroxide monohydrate (0.02 g, 0.48 mmol) was added to the stirred mixture at r.t. The mixture was heated at 45 °C for 18 h, then cooled to r.t. and diluted with petrol/EtOAc (7:2, 5 mL), followed by the dropwise addition of sat. aq. potassium hydrogen sulfate (10 mL) to pH 1. The aqueous layer was extracted with warm petrol/EtOAc (7:2, 3 × 10 mL). The combined organic layers were dried and concentrated. Column chromatography, eluting with petrol/EtOAc (7:2) gave the title compound **23**.

Yield: 0.019 g (64%); white solid; mp 51–53 °C; R_f 0.42 (above solvent); $[\alpha]_D^{21}$ +2.5 (*c* 1.4, $CHCl_3$).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{78}H_{152}O_3Na$: 1160.1634; found: 1160.1626.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.73 (td, *J* = 4.8, 7.9 Hz, 1 H), 2.48 (td, *J* = 5.4, 8.9 Hz, 1 H), 1.76–1.71 (m, 1 H), 1.63–1.60 (m, 2 H), 1.54–1.47 (m, 4 H), 1.26 (m, 129 H), 0.89 (t, *J* = 6.9 Hz, 6 H), 0.66–0.62 (m, 4 H), 0.57 (dt, *J* = 4.1, 8.2 Hz, 2 H), –0.33 (q, *J* = 4.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.6, 72.1, 50.8, 36.6, 31.9, 30.2, 29.7, 29.6, 29.5, 29.4, 28.7, 27.3, 25.7, 22.7, 15.8, 14.1, 10.9.

IR: 3281, 2919, 2852, 1709, 1466, 1377, 721 cm^{-1}.

(*R*)-2-((*R*)-1-Hydroxy-12-[(1*R*,2*S*)-2-[14-((1*S*,2*R*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl]dodecyl)hexacosanoic Acid (24)

(a) LiHMDS (0.32 mL, 0.34 mmol) was added to a stirred solution of aldehyde **20** (0.17 g, 0.24 mmol) and sulfone **19** (0.20 g, 0.26 mmol) in anhydrous THF (5 mL) at –10 °C under nitrogen, then stirred at r.t. for 1.5 h. Water (10 mL) was added and the mixture was extracted with petrol/ether (1:1, 3 × 10 mL) and the combined organic layers were washed with sat. aq. sodium hydroxide (2 × 5 mL), and concentrated. Column chromatography, eluting with petrol/EtOAc (20:1), gave (*R*)-2-((*E*/*Z*)-(*R*)-1-(*tert*-butyldimethylsilanyloxy)-12-[(1*S*,2*R*)-2-[14-((1*R*,2*S*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl]dodec-11-enyl)hexacosanoic acid methyl ester (0.13 g, 40%).

(b) Dipotassium azodicarboxylate (2.0 g, 10.3 mmol) was added to a stirred solution of the derived alkenes (0.11 g, 0.09 mmol) in anhydrous THF (3 mL) and MeOH (1.5 mL) and then cooled to 0 °C under nitrogen. Glacial acetic acid (0.5 mL) was dissolved in THF (1.0 mL), and then added dropwise to the mixture, which was stirred overnight at r.t. The process was repeated using the same amount of glacial acetic acid in THF until there was a change in colour from bright yellow to off-white. The reaction was worked up and purified as before to give (*R*)-2-(*R*)-2-((*R*)-1-(*tert*-butyldimethylsilanyloxy)-12-[(1*R*,2*S*)-2-[14-((1*S*,2*R*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl]dodecyl)hexacosanoic acid methyl ester.

Yield: 0.1 g (90 %); thick oil.

MALDI MS: *m*/*z* [M + Na]$^+$ calcd for $C_{85}H_{168}O_3SiNa$: 1288.3; found: 1288.5.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (td, *J* = 4.8, 6.5 Hz, 1 H), 3.66 (s, 3 H), 2.54 (ddd, *J* = 3.8, 7.3, 10.8 Hz, 1 H), 1.56–1.14 (m, 134 H), 0.89 (t, *J* = 6.6 Hz, 6 H), 0.85 (s, 9 H), 0.66–0.65 (m, 4 H), 0.55 (dt, *J* = 4.1, 8.2 Hz, 2 H), 0.05 (s, 3 H), 0.03 (s, 3 H), –0.33 (q, *J* = 4.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.1, 73.3, 51.4, 33.7, 31.9, 30.2, 29.8, 29.7, 29.67, 29.6, 29.5, 29.4, 28.7, 27.8, 25.8, 23.7, 22.7, 18.0, 15.8, 14.1, 10.9, –4.3, –4.9.

IR: 2924, 2853, 1742, 1465, 1254 cm^{-1}.

(c) A dry polyethylene vial equipped with an acid-resistant rubber septum was charged with the above ester (0.1 g, 0.08 mmol) and anhydrous pyridine (0.1 mL) in anhydrous THF (4 mL) and stirred at r.t. under nitrogen. To it was added hydrogen fluoride-pyridine complex (ca. 70% hydrogen fluoride, 0.7 mL) at 5 °C. The mixture was then stirred at 45 °C for 17 h, then diluted with petrol/ether 10:1 (30 mL) and worked up as before to give (*R*)-2-((*R*)-1-hydroxy-12-[(1*R*,2*S*)-2-[14-((1*S*,2*R*)-2-eicosylcyclopropyl)tetradecyl]cyclopropyl]dodecyl)hexacosanoic acid methyl ester.

Yield: 0.04 g (44%); white solid; mp 55–57 °C; $[\alpha]_D^{19}$ +2.4 (*c* 2.0, $CHCl_3$).

MALDI MS: *m*/*z* [M + Na]$^+$ calcd for $C_{79}H_{154}O_3Na$: 1174.2; found: 1174.4.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.72 (s, 3 H), 3.68–3.62 (m, 1 H), 2.46–2.41 (m, 1 H), 1.75–1.68 (m, 1 H), 1.62–1.57 (m, 2 H), 1.49–1.14 (m, 132 H,), 0.88 (t, *J* = 7.3 Hz, 6 H), 0.68–0.62 (m, 4 H), 0.58 (dt, *J* = 3.8, 8.1 Hz, 2 H), –0.33 (q, *J* = 5.0 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.2, 72.3, 51.2, 35.7, 31.9, 30.2, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 27.4, 25.7, 22.7, 15.8, 14.1, 10.9.

IR: 3520, 2924, 2855, 2367, 1712, 1461, 1377, 1165, 721 cm^{-1}.

(d) The above methyl ester (0.040 g, 0.035 mmol) was dissolved in THF (4.0 mL), MeOH (0.5 mL) and water (0.7 mL), and then lithium hydroxide monohydrate (0.02 g, 0.48 mmol) was added with stirring at r.t. The reaction was heated to reflux at 45 °C for 18 h, then cooled to r.t. and worked up purified as before to give the title compound **24**.

Yield: 0.033 g (84%); white solid; mp 52–53 °C; R_f 0.42 (7:2, petrol/EtOAc); $[\alpha]_D^{21}$ +2.5 (*c* 1.7, $CHCl_3$).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{78}H_{152}O_3Na$: 1160.1634; found: 1160.1627.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74 (td, *J* = 4.8, 7.9 Hz, 1 H), 2.47 (td, *J* = 5.4, 8.8 Hz, 1 H), 1.78–1.72 (m, 1 H), 1.67–1.60 (m, 2 H), 1.54–1.47 (m, 4 H), 1.45–1.07 (m, 129 H), 0.88 (t, *J* = 6.9 Hz, 6 H), 0.67–0.64 (m, 4 H), 0.57 (dt, *J* = 4.1, 8.2 Hz, 2 H), –0.33 (q, *J* = 4.9 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.5, 72.1, 50.7, 35.5, 31.9, 30.2, 29.8, 29.7, 29.65, 29.55, 29.5, 29.44, 29.4, 28.6, 27.4, 25.7, 22.6, 15.9, 14.0, 10.8.

IR: 3317, 2922, 2852, 1681, 1464, 1377, 721 cm^{-1}.

5-((*S*)-3-((1*R*,2*R*)-2-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1*H*-tetrazole (27)

(a) Diethyl azodicarboxylate (10.6 g, 60.8 mmol) in anhydrous THF (15 mL) was added to a stirred solution of (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol **26**[26] (10.0 g, 46.7 mmol), triphenylphosphine (17.2 g, 65.5 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (11.6 g, 65.0 mmol) in anhydrous THF (100 mL) at 0 °C, allowed to reach r.t. and stirred overnight, then the solvent was evaporated and the residue was heated at reflux with petroleum/EtOAc (5:2, 150 mL) for 1 h and filtered. The filtrate was evaporated; column chromatography eluting with petroleum/EtOAc (5:2) gave 5-((*S*)-3-((1*R*,2*R*)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylthio)-1-phenyl-1*H*-tetrazole.

Yield: 16 g (91%); pale-yellow oil; $[\alpha]_D^{22}$ –34 (*c* 1.4, $CHCl_3$).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{26}N_4NaO_2S$: 397.1674; found: 397.1630.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.49 (m, 5 H), 4.0 (dd, *J* = 6.0, 7.9 Hz, 1 H), 3.72 (br q, *J* = 7.8 Hz, 1 H), 3.62 (br.t, *J* = 7.6 Hz, 1 H), 3.50–3.45 (m, 1 H), 3.31–3.25 (m, 1 H), 1.84–1.73 (m, 1 H), 1.71–1.67 (m, 1 H), 1.39 (s, 3 H), 1.28 (s, 3 H), 1.24–1.20 (m, 1 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 0.96–0.91 (m, 1 H), 0.82 (dt, *J* = 5.6, 8.5 Hz, 1 H), 0.79–0.69 (m, 1 H), 0.25 (br q, *J* = 5.6 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.2, 154.2, 133.6, 130.1, 129.7, 123.8, 108.4, 77.2, 70.0, 36.5, 32.9, 30.9, 26.8, 25.7, 23.4, 19.5, 19.2, 8.6.

IR: 2984, 2831, 1597, 1500, 1379, 1059, 853, 761 cm^{-1}.

(b) A solution of ammonium molybdate(VI) tetrahydrate (24.7 g, 20.0 mmol) in 35% H_2O_2 (40 mL) was cooled in an ice bath and added to a stirred solution of the above tetrazole (15.0 g, 40.0 mmol) in THF (140 mL) and IMS (300 mL) at 10 °C and stirred at r.t. for 2 h. A further solution of ammonium molybdate(VI) tetrahydrate (12.4 g, 10.0 mmol) in 35% H_2O_2 (20 mL) was added and the mixture was stirred at r.t. for 18 h. The mixture was poured into water (1.5 L) and extracted with CH_2Cl_2 (1 × 300 mL, 3 × 50 mL). The combined organic layers were washed with water (500 mL), and the solvent was evaporated. Column chromatography eluting with petroleum/EtOAc (5:2 then 1:1) gave the title compound **27**.

Yield: 14 g (87%); yellow oil; $[\alpha]_D^{20}$ –37 (*c* 1.8, $CHCl_3$).

MS: *m*/*z* found [M + Na]$^+$: 429.1528; $C_{19}H_{26}N_4NaO_4S$ requires: 429.1572.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 2 H), 7.60–7.54 (m, 3 H), 4.08 (br dd, *J* = 5.4, 7.8 Hz, 1 H), 3.82–3.76 (m, 2 H), 3.70 (dd, *J* = 5.5, 10.1 Hz, 1 H), 3.64 (t, *J* = 7.8 Hz, 1 H), 2.03–1.96 (m, 1 H), 1.86–1.78 (m, 1 H), 1.39 (s, 3 H), 1.37–1.33 (m, 1 H), 1.30 (s, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 0.99–0.92 (m, 1 H), 0.82 (dt, *J* = 4.7, 8.8 Hz, 1 H), 0.72–0.66 (m, 1 H), 0.31 (br q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.2, 132.8, 131.3, 129.5, 124.9, 108.4, 76.2, 69.8, 53.8, 32.0, 30.7, 28.7, 26.6, 25.5, 22.8, 19.5, 19.1, 8.1.

IR: 2985, 2834, 1595, 1498, 1339, 1152, 1059, 853, 764 cm^{-1}.

(*S*)-2,2-Dimethyl-4-((1*R*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)-1,3-dioxolane (28)

LiHMDS (14.6 mL, 15.0 mmol, 1.06 M) was added dropwise to a stirred solution of aldehyde **25** (4.3 g, 9.0 mmol) and sulfone **27** (4.2 g, 10.3 mmol) in anhydrous THF (50 mL) under nitrogen at –10 °C. The mixture was allowed to reach r.t. and stirred for 2 h, then worked up as above to give (*S*)-2,2-dimethyl-4-((1*R*,2*R*)-2-[(*E*/*Z*)-((*S*)-16-

((1*S*,2*R*)-2-octadecylcyclopropyl)hexa-dec-3-en-2-yl)]cyclopropyl)-1,3-dioxolane (4.6 g, 78%) as a colourless oil. Dipotassium azodicarboxylate (4.5 g, 23.2 mmol) was added to a stirred solution of the above [1,3]-dioxolane (4.6 g, 7.0 mmol) in THF (40 mL) and MeOH (15 mL) under nitrogen at 10 °C. A solution of glacial acetic acid (6 mL) and THF (6 mL) was added dropwise for 24 h then additional dipotassium azodicarboxylate (2.3 g, 11.6 mmol) and a solution of glacial acetic acid (3 mL) and THF (3 mL) were added and stirred for a further 24 h. The reaction was worked up as above to give the title compound **28**.

Yield: 3.9 g (84%); thick oil; $[\alpha]_D^{22}$ –8.5 (*c* 0.6, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{45}H_{86}O_2Na$: 681.6526; found: 681.6556.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.13–4.06 (m, 1 H), 3.75–3.65 (m, 2 H), 1.45 (s, 3 H), 1.37–1.13 (br m, including 3 H s at δ 1.36, 67 H), 0.99 (br s, 3 H), 0.88 (t, *J* = 6.3 Hz, 3 H), 0.83 (dt, *J* = 4.5, 8 Hz, 1 H), 0.71–0.65 (m, 3 H), 0.57 (dt, *J* = 4.1, 8.5 Hz, 1 H), 0.23 (br q, *J* = 5.4 Hz, 1 H), –0.33 (br q, *J* = 5.1 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 108.2, 77.9, 70.0, 37.4, 33.2, 31.9, 30.0, 29.6, 29.3, 28.7, 27.1, 26.8, 25.7, 23.8, 22.6, 20.0, 19.2, 15.7, 14.1, 10.9, 9.0.

IR: 2928, 2848, 1607, 1467, 1369, 1159, 1063, 824, 720 cm^{-1}.

cis-(1*R*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-Octadecylcyclopropyl)hexadecane-2-yl)cyclopropanecarbaldehyde (29)

Periodic acid (3.3 g, 17.1 mmol) was added to stirred solution of the acetal **28** (3.8 g, 5.8 mmol) in anhydrous ether (60 mL) under nitrogen at r.t. The mixture was stirred for 16 h, then worked up as above to give the aldehyde **29**.

Yield: 3.1 g (94%); white solid; mp 37–38 °C; $[\alpha]_D^{22}$ –0.015 (*c* 1.2, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{41}H_{78}ONa$: 609.5950; found: 609.5924.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.33 (br d, *J* = 5.7 Hz, 1 H), 1.94–1.87 (m, 1 H), 1.37–1.14 (br m, 66 H), 1.05 (br d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 6.5 Hz, 3 H), 0.68–0.60 (m, 2 H), 0.56 (dt, *J* = 4.1, 8.2 Hz, 1 H), –0.33 (br q, *J* = 5.1 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.7, 37.4, 32.5, 32.2, 31.9, 30.2, 29.8, 29.6, 29.5, 29.4, 29.3, 29.1, 28.8, 28.7, 28.5, 26.7, 22.6, 20.1, 15.7, 14.1, 13.6, 10.8.

IR: 2920, 2849, 1692, 1468, 1402, 825, 720 cm^{-1}.

trans-(1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-Octadecylcyclopropyl)hexadecan-2-yl)cyclopropanecarbaldehyde (30)

Sodium methoxide (0.60 g, 11 mmol) was added to a stirred solution of *cis*-aldehyde **29** (3.5 g, 6.0 mmol) in MeOH (20 mL) and THF (30 mL) and heated at reflux for 56 h. The mixture was cooled to r.t. and worked up as above to give the *trans*-aldehyde **30**.

Yield: 2.7 g (77%); semi-solid; $[\alpha]_D^{20}$ +8.5 (*c* 1.0, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{41}H_{78}ONa$: 609.5950; found: 609.5938.

^1H NMR (500 MHz, $CDCl_3$): 8.99 (d, *J* = 5.7 Hz, 1 H), 1.71–1.66 (m, 1 H), 1.38–1.17 (br m, 65 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.95–0.91 (m, 1 H), 0.88 (br t, *J* = 6.9 Hz, 3 H), 0.69–0.64 (m, 2 H), 0.56 (dt, *J* = 4.1, 8.2 Hz, 1 H), –0.33 (q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.0, 36.8, 31.9, 30.4, 30.2, 29.8, 29.6, 29.6, 29.3, 29.3, 28.7, 27.0, 22.6, 19.3, 15.7, 14.1, 13.2, 10.9.

IR: 2917, 2810, 1698, 1471, 1376, 1170, 1035, 925, 718 cm^{-1}.

16-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-Octadecylcyclopropyl)hexadecan-2-yl)cyclopropyl)hexadecanal (33)

(a) LiHMDS (6.8 mL, 7.2 mmol, 1.06 M) was added dropwise to a stirred solution of *trans*-aldehyde **30** (2.7 g, 4.6 mmol) and 15-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)pentadecyl pivalate **32** (2.5 g, 4.8 mmol) in anhydrous THF (30 mL) under nitrogen at –10 °C. The mixture was allowed to reach r.t. and stirred for 2 h, then worked up as above to give a thick oil, which solidified later as a mixture of (*E*/*Z*)-16-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadec-ane-2-yl)cyclopropyl)hexadec-15-enyl pivalates (3.8 g, 94%). Dipotassium azodicarboxylate (4.5 g, 23 mmol) was added to a stirred solution of the above alkene (3.8 g, 4.3 mmol) in THF (30 mL) and MeOH (15 mL) under nitrogen at 10 °C. A solution of glacial acetic acid (6 mL) and THF (6 mL) was added dropwise for 24 h then additional dipotassium azodicarboxylate (2.3 g, 11.6 mmol) and a solution of glacial acetic acid (3 mL) and THF (3 mL) were added and stirred for a further 24 h. The reaction was worked up as above to give 16-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)hexadecyl pivalate.

Yield: 2.78 g (73%); colourless oil; $[\alpha]_D^{22}$ +4.04 (*c* 1.46, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{61}H_{118}O_2Na$: 905.9030; found: 905.9051.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.05 (br t, *J* = 6.6 Hz, 2 H), 1.67–1.58 (m, 4 H), 1.38–1.26 (br m, 88 H), 1.20 (s, 9 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H), 0.69–0.64 (m, 3 H), 0.56 (dt, *J* = 3.9, 7.8 Hz, 1 H), 0.48–0.42 (m, 1 H), 0.21–0.09 (m, 3 H), –0.32 (br q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 178.6, 64.4, 38.7, 38.1, 37.4, 34.4, 31.9, 30.2, 30.0, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 28.7, 28.6, 27.2, 27.2, 26.1, 25.9, 26.1, 25.9, 22.6, 22.3, 19.6, 18.6, 15.8, 14.0, 10.9, 10.4.

IR: 2920, 2810, 1732, 1470, 1153 cm^{-1}.

(b) The above pivalate (2.78 g, 3.13 mmol) was added to a stirred solution of potassium hydroxide (0.7 g, 12.5 mmol) dissolved in a mixture of THF/MeOH/water (30:20:5 mL). The mixture was stirred at 70 °C for 3 h, then worked up as above to give 16-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)hexadecan-1-ol.

Yield: 1.5 g (60%); white solid; mp 50–52 °C; $[\alpha]_D^{22}$ +3.8 (*c* 1.1, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{56}H_{110}ONa$: 821.8454; found: 821.8462.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.65 (br t, *J* = 6.6 Hz, 2 H), 1.62–1.54 (m, including br s for hydroxyl group, 10 H), 1.37–1.17 (br m, 83 H), 0.9 (d, *J* = 6.6 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.68–0.62 (m, 3 H), 0.57 (dt, *J* = 3.8, 7.9 Hz, 1 H), 0.47–0.42 (m, 1 H), 0.22–0.09 (m, 3 H), –0.32 (br q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 63.1, 38.1, 37.4, 34.4, 32.8, 31.9, 30.2, 30.0, 29.7, 29.6, 29.4, 29.3, 28.7, 27.2, 26.1, 25.7, 22.6, 19.6, 18.6, 15.8, 14.0, 10.9, 10.4.

IR: 3419, 2918, 2845, 1471, 1366, 1057, 898, 719 cm^{-1}.

(c) The above alcohol (1.50 g, 1.9 mmol) was dissolved in hot CH_2Cl_2 (20 mL) and added to a refluxing stirred suspension of PCC (0.94 g, 4.4 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred vigorously for 2 h, then worked up as above to give aldehyde **33**.

Yield: 1.24 g (85%); white solid; mp 40–42 °C; $[\alpha]_D^{24}$ +5.9 (*c* 1.0, $CHCl_3$).

MS: *m*/*z* $[M + Na]^+$ calcd for $C_{56}H_{108}ONa$: 819.8298; found: 819.8280.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 1.9 Hz, 1 H), 2.42 (dt, *J* = 1.9, 7.2 Hz, 2 H), 1.63 (br pent, *J* = 7.2 Hz, 2 H), 1.42–1.23 (br m, 78 H), 1.21–1.09 (m, 10 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H), 0.69–0.64 (m, 3 H), 0.57 (dt, *J* = 4.1, 8.2 Hz, 1 H), 0.47–0.42 (m, 1 H), 0.22–0.09 (m, 3 H), –0.32 (br q, *J* = 5.1 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 202.8, 43.9, 38.1, 37.4, 34.4, 31.9, 30.2, 30.0, 29.7, 29.6, 29.6, 29.4, 29.3, 29.1, 29.0, 28.7, 27.6, 27.2, 26.1, 22.6, 22.1, 20.4, 19.6, 19.4, 18.6, 15.7, 14.2, 14.0, 11.4, 10.9, 10.4.

IR: 2920, 2810, 1707, 1470, 1019, 845, 718 cm^{-1}.

Methyl (*R*)-2-((*R*)-1-(*tert*-Butyldimethylsilyloxy)-19-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoate (36)

LiHMDS (2.4 mL, 2.5 mmol, 1.06 M) was added dropwise to a stirred solution of aldehyde **33** (1.2 g, 1.5 mmol) and methyl (*R*)-2-((*R*)-1-(*tert*-butyldimethylsilyloxy)-3-(1-phenyl-1*H*-tetrazol-5-ylthio)propyl)tetracosanoate **35**[35] (1.27 g, 1.60 mmol) in anhydrous THF (30 mL) under nitrogen at –10 °C. The reaction was allowed to reach r.t. and stirred for 2 h, then worked up as above to give a colourless oil as a mixture of (*E*/*Z*) methyl (*R*)-2-((*R*)-1-(*tert*-butyldimethylsilyloxy)-19-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadec-4-enyl)tetracosanoates (1.7 g, 85%). Dipotassium azodicarboxylate (2.0 g, 10.3 mmol) was added to a stirred solution of the above alkenes (2.5 g, 1.9 mmol) in THF (25 mL) and MeOH (15 mL) at 5 °C. A solution of glacial acetic acid (3 mL) and THF (3 mL) was added dropwise for 24 h then additional dipotassium azodicarboxylate (1.5 g, 7.7 mmol) and a solution of glacial acetic acid (2 mL) and THF (2 mL) were added and stirred for a further 24 h. The mixture was worked up as above to give methyl (*R*)-2-((*R*)-1-(*tert*-butyldimethylsilyloxy)-19-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoate **36**.

Yield: 1.41 g (83%); colourless oil; $[\alpha]_D^{25}$ +4.3 (*c* 0.81, $CHCl_3$).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{90}H_{178}O_3SiNa$: 1358.3443; found: 1358.3410.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.92–3.89 (m, 1 H), 3.66 (s, 3 H), 2.53 (ddd, *J* = 3.7, 7.2, 11.0 Hz, 1 H), 1.57 (br s, 8 H), 1.37–1.10 (br m, 132 H), 0.91–0.84 (m, including d integrating to 3 H, t integrating to 6 H and s integrating to 9 H, 18 H), 0.70–0.65 (m, 3 H), 0.56 (dt, *J* = 3.7, 8.1 Hz, 1 H), 0.48–0.42 (m, 1 H), 0.21–0.078 (m, 3 H), 0.049 (s, 3 H), 0.025 (s, 3 H), –0.32 (br q, *J* = 5.1 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.1, 73.2, 51.5, 51.1, 38.1, 37.4, 33.7, 31.9, 30.2, 30.0, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 28.7, 27.5, 27.2, 26.1, 25.7, 23.7, 22.6, 19.6, 18.6, 17.9, 15.7, 14.1, 10.9, 10.4, –4.3, –4.9.

IR: 2923, 2813, 1741, 1465, 1361, 1254, 1166, 836, 775 cm^{-1}.

(*R*)-2-((*R*)-1-Hydroxy-19-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoic Acid (37)

(a) Ester **36** (1.41 g, 1.05 mmol) was dissolved in anhydrous THF (15 mL) in a anhydrous polyethylene vial and stirred under nitrogen at r.t. Pyridine (0.3 mL) and hydrogen fluoride-pyridine complex (1.1 mL, 0.77 mmol) were added and the mixture was stirred for 17 h at 45 °C, then worked up as above to give methyl (*R*)-2-((*R*)-1-hydroxy-19-((1*S*,2*R*)-2-((*S*)-16-((1*S*,2*R*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoate.

Yield: 0.92 g (72%); white solid; mp 48–49 °C; $[\alpha]_D^{23}$ +8.6 (*c* 0.18, $CHCl_3$).

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{84}H_{164}O_3Na$: 1244.2578; found: 1244.2605.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.70–3.66 (m, 1 H), 2.46–2.40 (m, 1 H), 1.74–1.69 (m, 1 H, for OH), 1.26–1.13 (br m, 140 H), 0.90–0.81 (m, including d integrating to 3 H and t integrating to 6 H, 9 H), 0.70–0.65 (m, 3 H), 0.57 (dt, *J* = 4.1, 7.9 Hz, 1 H), 0.48–0.42 (m, 1 H), 0.22–0.09 (m, 3 H), –0.31 (br q, *J* = 5.1 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.2, 72.3, 51.4, 50.9, 38.1, 37.4, 35.7, 34.4, 31.9, 30.3, 30.2, 30.0, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 28.8, 28.7, 27.4, 27.2, 26.1, 25.7, 22.6, 22.6, 22.3, 19.6, 18.6, 15.7, 14.1, 10.9, 10.4.

IR: 3420, 2917, 2810, 1715, 1618, 1468, 1375, 1196, 720 cm^{-1}.

(b) Lithium hydroxide monohydrate (0.47 g, 11.2 mmol) was added to a stirred solution of the above ester (0.92 g, 7.5 mmol) in THF (12 mL), MeOH (1.5 mL) and water (2 mL) at r.t. The mixture was stirred at 45 °C for 18 h, then cooled to r.t. and worked up as above to give the title acid **37**.

Yield: 0.63 g (70%); white solid; mp 55–56 °C; R_f 0.42 (7:2 petrol/EtOAc); $[\alpha]_D^{22}$ +5.2 (*c* 0.50, $CHCl_3$).

MALDI MS: *m*/*z* [M + Na]$^+$ calcd for $C_{83}H_{162}O_3Na$: 1230.25; found: 1230.24.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74–3.71 (m, 1 H), 2.47 (td, *J* = 5.0, 10.4 Hz, 1 H), 1.69–1.58 (m, 2 H), 1.55–1.47 (m, 2 H), 1.41–1.34 (m, 4 H), 1.24–1.01 (br m, 134 H), 0.9 (d, *J* = 6.6 Hz, 3 H, α-Me), 0.88 (t, *J* = 6.6 Hz, 6 H, terminal 2 × CH_3), 0.70–0.64 (m, 3 H, 2 × C*H*-*cis*-cyclopropane and *CH*CH_3), 0.57 (dt, *J* = 3.7, 7.8 Hz, 1 H), 0.48–0.42 (m, 1 H), 0.22–0.09 (m, 3 H), –0.32 (br q, *J* = 5.1 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.5, 72.1, 50.7, 38.1, 37.4, 35.5, 34.5, 31.9, 30.2, 30.0, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 28.7, 27.3, 27.2, 26.1, 25.7, 22.6, 19.6, 18.6, 15.7, 14.1, 10.9, 10.4.

IR: 3411, 2919, 2810, 1689, 1470, 1191, 1016, 720 cm^{-1}.

(*R*)-2-((*R*)-1-Hydroxy-19-((1*S*,2*R*)-2-((*S*)-16-((1*R*,2*S*)-2-Octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoic Acid (38)

(a) Methyl (*R*)-2-((*R*)-1-(*tert*-Butyldimethylsilyloxy)-19-((1*S*,2*R*)-2-((*S*)-16-((1*R*,2*S*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoate (see the Supporting Information) (0.95 g, 0.71 mmol) was dissolved in anhydrous THF (12 mL) in a dry polyethylene vial and stirred under nitrogen at r.t. Pyridine (0.2 mL) and hydrogen fluoride-pyridine complex (0.7 mL, 0.47 mmol) were added and the mixture was stirred for 17 h at 45 °C, then diluted with petroleum/EtOAc (10:1, 70 mL) and neutralised with sat. aq. $NaHCO_3$ until no more carbon dioxide was liberated. The aqueous layer was re-extracted with petroleum/EtOAc (10:1, 2 ×50 mL). The combined organic layers were washed with brine, dried and evaporated; column chromatography eluting with petroleum/EtOAc (20:1) gave methyl (*R*)-2-((*R*)-1-hydroxy-19-((1*S*,2*R*)-2-((*S*)-16-((1*R*,2*S*)-2-octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoate.

Yield: 0.73 g (72%); white solid; mp 47–48 °C; $[\alpha]_D^{22}$ +8.1 (*c* 0.19, $CHCl_3$) .

MS: *m*/*z* [M + Na]$^+$ calcd for $C_{84}H_{164}O_3Na$: 1244.2578; found: 1244.2612.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 3.68–3.63 (m, 1 H), 2.49–2.36 (m, 1 H), 2.05 (br s, 1 H, for hydroxyl group), 1.37–1.14 (br m, 140 H), 0.90–0.81 (m, including d integrating to 3 H and t integrating to 6 H, 9 H), 0.68–0.63 (m, 3 H), 0.57 (dt, *J* = 4.1, 7.8 Hz, 1 H), 0.48–0.42 (m, 1 H), 0.21–0.10 (m, 3 H), –0.31 (br q, *J* = 5.3 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.2, 72.3, 51.4, 50.9, 38.1, 37.4, 36.3, 35.7, 34.5, 34.1, 33.7, 31.9, 31.5, 30.3, 30.2, 30.0, 29.7, 29.5, 29.4, 29.3, 29.0, 28.8, 28.7, 27.6, 27.4, 27.2, 26.1, 25.8, 25.7, 22.6, 22.3, 22.1, 20.4, 19.6, 19.4, 18.6, 15.7, 14.2, 14.1, 14.0, 11.7, 10.9, 10.4, 8.8.

IR: 3419, 2917, 2810, 1712, 1618, 1470, 1375, 1197, 719 cm^{-1}.

(b) Lithium hydroxide monohydrate (0.38 g, 9.1 mmol) was added to a stirred solution of the above methyl ester (0.73 g, 0.61 mmol) in THF (12 mL), MeOH (1.5 mL) and water (2 mL) at r.t. The mixture was stirred at 45–50 °C for 18 h, then cooled to r.t. and quenched with sat. aq. NH_4Cl (15 mL) then acidified to pH 1 with 5 % HCl and the product was extracted with petroleum/EtOAc (5:1, 3 × 30 mL). The combined organic layers were washed with water (20 mL), dried and evaporated. Column chromatography eluting with petroleum/EtOAc (7:2) gave the title acid **38**.

Yield: 0.61 g (84%); white solid; mp 54–55 °C; R_f 0.42 (above solvent); $[\alpha]_D^{24}$ +5.5 (*c* 0.60, $CHCl_3$).

MALDI MS: *m*/*z* found $[M + Na]^+$: 1230.2; $C_{83}H_{162}O_3Na$ requires: 1230.2.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.74–3.71 (m, 1 H), 2.47 (td, *J* = 5.0, 9.7 Hz, 1 H), 1.76–1.49 (m, 21 H), 1.58–1.14 (br m, 121 H), 0.9 (d, *J* = 6.9 Hz, 3 H, α-Me), 0.88 (t, *J* = 6.6 Hz, 6 H, terminal 2 × CH_3), 0.69–0.61 (m, 3 H, 2 × *CH*-*cis*-cyclopropane and *CH*CH_3), 0.57 (dt, *J* = 4.1, 8.2 Hz, 1 H), 0.46–0.42 (m, 1 H), 0.22–0.09 (m, 3 H), –0.32 (br q, *J* = 5.4 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 179.5, 72.1, 50.8, 38.1, 37.4, 35.5, 34.5, 31.9, 30.2, 30.0, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 28.7, 27.3, 27.2, 26.1, 25.7, 22.6, 19.6, 18.6, 15.7, 14.1, 10.9, 10.4.

IR: 3418, 2918, 2819, 1685, 1470, 1205, 1020, 719 cm^{-1}.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588556.

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