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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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Abstract We report the synthesis of three stereoisomers of a mycolic acid 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

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 CHMCO- fragment (keto-MA). Structural assignment has often been based on mass spectra of mixtures of homologues or fragments from them.8 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 α–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-MA 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)
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.

The stereochemistry B of the trans-cyclopropane unit is consistent with NMR spectra and optical rotations of this fragment in methoxy-MA, 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, 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.

The proximal cyclopropane unit 11 was treated with aldehyde 9 in a modified Julia reaction, 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 alkenes using di-imide, gave a single enantiomer of alcohol 12 (Scheme 4).

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

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).

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

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).

The "H and 13C 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 ([α]D +3.7), as a mixture of homologues in which 2 predominates. The specific rotation of the synthetic material 2a, protected in the same way ([α]D +4.2) was close to that of the natural mixture. The specific rotation of the synthetic free acid 2a was [α]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. 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. 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 MA containing trans-cyclopropane and a distal cis-cyclopropane do not appear to be present in Mtb, they are present in other Mycobacteria such as Mycobacterium kansasi and Mycobacterium avium complex.
We therefore describe the synthesis of two stereoisomers of one such compound. The aldehyde 25 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).

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

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. The trans-cyclopropane 38 is moderately stimulatory, while 37 has a smaller effect.

MA are present both as bound tetramycyl pentarabinoose clusters and as extractable trehalose 6,6′-dimycolates (‘cord factor’). The MA 37 and 38 were converted into the corresponding TDM and TMM (see the Supporting Information) using methods described before. 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. Moreover, they are recognised by antibodies in the serum of patients with pulmonary tuberculosis, providing the basis of a diagnostic assay.

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 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. [α]D values were recorded in CHCl3 with a POLAR 2001 Optical Activity polarimeter. Mass spectra were recorded with a Bruker-MALDI-TOF MS.
(1R,2S)-2-Eicosyclopropanecarbaldehyde (6)

(a) 5-((Nonadec-1-yl)-1-phenyl-1H-tetrazole 4 (15.0 g, 0.032 mol) and butyric acid (1R,2S)-cis-2-formylcyclopropyl) methyl ester 5 (4.8 g, 0.028 mol) was 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 (2 × 100 mL), dried and evaporated to obtain a residue; column chromatography, eluting with petrol/EtOAc (20:1) gave butyric acid (2E)-1S-2-icocylopropyl)cyclopropyl)methyl ester (9.5 g, 80%) as 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) 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. ammonium chloride (200 mL) in anhydrous THF (50 mL) at −10 °C under nitrogen. The mixture was heated to reach reflux at 100 °C for 2 h, then worked up and purified as before to give (E/Z)-1S-2-icocylopropyl)cyclopropyl)methyl ester (6.4 g, 90%) 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)-1S-2-icocylopropyl)cyclopropyl)methyl ester (5.2 g, 83%) as a white solid. Hydrazine monohydrate (20 mL), acetic acid (2 mL), and sat. aq. copper sulphate (2 mL) were added in succession to the derived esters (5.0 g, 9.7 mmol) in isopropanol (250 mL) at 80 °C, and 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; [α]D [26] +0.33 (c 2.03, CHCl3).

1H NMR (500 MHz, CDCl3): 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 (dt, J = 4.7, 8.2 Hz, 1 H), −0.01 (q, J = 5.2 Hz, 1 H).

13C NMR (126 MHz, CDCl3): 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: 3162, 2922, 1724, 1461, 1114, 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 rt. The mixture was stirred for 2 h at rt, 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 9.

Yield: 4.5 g (91%); [α]D [26] +3.8 (c 1.1, CHCl3) (enantiomer −3.9 (c 1.1, CHCl3)).

1H NMR (500 MHz, CDCl3): 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).
5-[13-((1R,2S)-2-Eicosylcyclopropyl)tridec-1-ene-1-sulfonyl]-phenyl-1H-tetrazole (10)

(a) 13-((1R,2S)-2-Eicosylcyclopropyl)tridec-1-ol 8 (4.0 g, 7.7 mmol) was dissolved in anhydrous THF (10 mL) together with trimethylphosphine (2.6 g, 10 mmol) and 1-phenyl-1H-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, and 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-((1R,2S)-2-Eicosylcyclopropyl)tridecyl-sulfonyl]phenyl-1H-tetrazole.

Yield: 5.1 g (97%); mp 42–44 °C; \([\alpha]_D^{22} -1.2 (c 1.3, \text{CHCl}_3)\).

MS: \(m/z [\text{M} + \text{Na}]^+ \text{calc} \) for C_{43}H_{76}N_{4}SNa: 703.5683; found: 703.5658.

\(^{1}H \text{NMR} (500 \text{MHz, CDCl}_3): \delta = 7.62–7.52 (m, 5 H), 3.42 (t, J = 7.4 \text{ Hz}, 2 H), 1.84 (pent, J = 7.5 \text{ Hz}, 2 H), 1.47 (pent, J = 7.3 \text{ Hz}, 2 H), 1.43–1.12 (m, 58 H), 0.91 (t, J = 6.9 \text{ Hz}, 3 H), 0.71–0.64 (m, 2 H), 0.59 (dt, J = 4.1, 8.3 \text{ Hz}, 1 H), -0.35 (q, J = 4.9 \text{ Hz}, 1 H).

\(^{13}C \text{NMR} (126 \text{ MHz, CDCl}_3): \delta = 154.8, 134.2, 133.4, 130.1, 125.3, 33.7, 30.2, 29.7, 29.65, 29.6, 29.5, 29.43, 29.4, 29.1, 28.73, 28.7, 22.9, 15.6, 14.4, 11.1.

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

(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 rt 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 hydratize 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.

Yield: 1.8 g (63%); white solid; mp 72–74 °C; \([\alpha]_D^{26} +8.3 (c 0.86, \text{CHCl}_3)\).

MS: \(m/z [\text{M} + \text{Na}]^+ \text{calc} \) for C_{41}H_{76}O_{3}Na: 611.6; found: 611.5980.


LiHMDS (3.7 mL, 4.0 mmol) was added to a stirred solution of butyric acid (1S,2R)-2-formylcyclopropyl)methyl ester 13 (0.5 g, 3.0 mmol) and siphone 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 (1S,2R)-2-[(E/Z)-14-[(1R,2S)-2-Eicosylcyclopropyl]tetradec-1-enyl]cyclopropyl)methyl ester (1.2 g, 62%) as a white solid in 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 (1S,2R)-2-[(E/Z)-14-[(1R,2S)-2-Eicosylcyclopropyl]tetradec-1-enyl]cyclopropyl)methyl ester (1.2 g, 62%) as a white solid.

MS: \(m/z [\text{M} + \text{Na}]^+ \text{calc} \) for C_{43}H_{80}ONa: 611.6; found: 611.5.
**SynOpen**  C. Don Lawson et al.

1H NMR (500 MHz, CDCl3): $\delta = 7.65 - 7.5$ (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).

13C NMR (126 MHz, CDCl3): $\delta = 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 tetrabenzyl (2.0 g, 2.7 mmol) in dichloromethane (100 mL), followed by the addition of a mixture of anhydrous 3-chloroperbenzoic acid 70% (1.67 g, 4.3 mmol, 2.5 equiv) in ChCl2 (50 mL). The reaction was stirred at r.t. for 48 h to give an off-white precipitate. Acidic hydroxyde (58, 80 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL) 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, CHCl3).

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

1H NMR (500 MHz, CDCl3): $\delta = 7.72 - 7.68$ (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, 4 H), 0.60 - 0.86 (including t at $\delta = 5.69$ 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).

13C NMR (126 MHz, CDCl3): $\delta = 153.7, 133.1, 131.4, 129.7, 125.2, 57.1, 31.9, 30.2, 29.6, 29.64, 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-[[152R,2]-[142S,2]-2-Eicosylcyclopropyl]tetradecyl)cyclopropylmethylsulfanyl]-1-phenyl-1H-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-1H-tetrazole-5-thiol (0.2 g, 1.1 mmol) were added. The mixture was cooled to 0 °C and treated with base (0.18 mL, 1.1 mmol) in anhydrous THF (5 mL). After stirring at r.t. overnight, the reaction mixture was worked up as before. Column chromatography eluting with dichloromethane gave 5-[[152R,2]-[142S,2]-2-Eicosylcyclopropyl]tetradecyl)cyclopropylmethylsulfanyl]-1-phenyl-1H-tetrazole.

Yield: 0.7 g (92%); mp 43–50 °C; $[\alpha]_D^{20} = -21$ (c 1.7, CHCl3).

MALDI MS: m/z [M + Na]$^+$ calc for $C_{48}H_{85}N_4O_2S$: 777.16; found: 777.14.

1H NMR (500 MHz, CDCl3): $\delta = 7.63 - 7.55$ (5, m, 5 H), 3.49 (d, $J = 7.9$ Hz, 2 H), 1.60 - 1.11 (including m at $J = 1.47 - 1.53$ 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, $J = 4.7$, 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).

13C NMR (125 MHz, CDCl3): $\delta = 133.8, 130.8, 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, 13 mmol) was added to a stirred solution of the above tetrabenzyl (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 to which petrol/ether 10:2 gave 5-

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1. **Synthetic Methodology**: The document describes the synthesis of a series of compounds, focusing on the chemical modifications of a specific molecule, highlighting the use of various organic chemistry techniques such as NMR and IR spectroscopy, column chromatography, and recrystallization. The text provides detailed procedures for the preparation and purification of these compounds, offering insights into the chemical transformations and properties observed.

2. **Structural Analysis**: Various NMR and IR spectra are provided, which are crucial for the structural identification of the compounds synthesized. These spectra help in confirming the chemical formulae and the molecular structure of the synthesized compounds.

3. **Experimental Procedures**: The document outlines the experimental procedures used, detailing the reagents, solvents, and experimental conditions. These are essential for reproducing the experiments and understanding the chemical reactions involved.

4. **Synthetic Applications**: The synthesized compounds have potential applications in various fields, such as medicinal chemistry or material science, depending on their structural properties and functional groups.

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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; [α]D20 +17 (c 1.2, CHCl3).

MALDI MS: m/z [M + Na]+ calcld for C85H168O3SiNa: 1288.3; found: 1288.4.

1H NMR (500 MHz, CDCl3): 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 cyclopropyl proton, 67 H), 0.92–0.97 (m, 1 H), 0.83 (t, J = 6.6 Hz, 3 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).

13C NMR (125 MHz, CDCl3): δ = 133.8, 129.9, 123.8, 35.0, 31.9, 30.1, 29.5, 28.7, 27.7, 17.9, 15.8, 14.6, 14.1, 12.5, 10.9.

IR: 2923, 2854, 1462, 1377, 1338, 1156 cm–1.

29.7, 29.5, 29.1, 28.7, 22.7, 15.9, 14.1, 11.4, 10.9, 8.0.

11C NMR (126 MHz, CDCl3): δ = 131.4, 129.7, 125.2, 57.1, 31.9, 30.2, 29.7, 29.5, 28.7, 22.7, 15.9, 14.1, 11.4, 10.9, 8.0.

Yield: 0.8 g (89%); mp 43–50 °C; [α]D20 +1.5 (c 1.4, CHCl3).

MALDI MS: m/z [M + Na]+ calcld for C85H168O3SiNa: 1288.3; found: 1288.4.

1H NMR (500 MHz, CDCl3): δ = 7.95–7.88 (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), 1.38–1.18 (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).

13C NMR (126 MHz, CDCl3): δ = 175.1, 73.2, 51.6, 51.2, 41.4, 36.1, 33.7, 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, 25.5, 25.8, 23.7, 22.7, 22.6, 20.5, 19.4, 18.0, 15.8, 14.1, 10.5, –4.4, –4.9.

IR: 2923, 2853, 1742, 1465, 1253 cm–1.

5-[(1R,2S)-2-[14-((1R,2S)-2-Eicosylcyclopropyl)tetradecyl]cyclopropylmethanesulfonyl]-1-phenyl-1H-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-1H-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; [α]D20 +1.5 (c 1.4, CHCl3).

MALDI MS: m/z [M + Na]+ calcld for C85H168O3SiNa: 1288.3; found: 1288.4.

(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; [α]D20 –18 (c 1.4, CHCl3).

MALDI MS: m/z [M + Na]+ calcld for C79H154O3Na: 1175.0; found: 1174.9.

Yield: 1.32 g (76%); [α]D20 +4.3 (c 0.94, CHC13).

MALDI MS: m/z [M + Na]+ calcld for C79H154O3Na: 1175.0; found: 1174.9.
(R)-2-[(R)-1-Hydroxy-12-[(1\(\alpha\))20]-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 tetradece 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) and dried and filtered. The filtrate was concentrated and the residue purified by column chromatography, eluting with petrol/EtOAc (7:2) to give compound 22.

Yield: 0.92 g (93%); \(\delta\) 4.02 (above solvent); \([\alpha]_{D}^{20} +2.0 (c 1.2, \text{CHCl}_3).\)

MS: \(m/z [M + Na]^+\) calc for C\(_{78}\)H\(_{152}\)O\(_3\)Na: 1161.06; found: 1160.59. \n
1H NMR (500 MHz, CDCl\(_3\)): \(\delta = 3.75-3.80 (m, 1 H), 1.74-1.84 (m, 136 H), 0.88 (t, \(J = 7.0 \text{ Hz}, 6 \text{ H}), 0.68-0.62 (m, 4 \text{ H}), 0.57 (dt, \(J = 4.1, 8.6 \text{ Hz}, 2 \text{ H}), -0.32 (q, \(J = 5.1 \text{ Hz}, 2 \text{ H}).\)

13C NMR (126 MHz, CDCl\(_3\)): \(\delta = 182.1, 72.1, 50.8, 35.5, 31.9, 30.2, 29.7, 29.66, 29.55, 29.42, 28.9, 27.3, 27.5, 22.7, 15.8, 14.1, 10.9.\)

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

(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 (7:2, 10 mL), followed by the dropwise addition of sat. aq. potassium hydrogen sulfate (20 mL), which brought the mixture to pH 1. The aqeous layer was separated and re-extracted with warm petrol/EtOAc (7:2, 3 × 10 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: 0.03 g (33%); white solid; mp 55-57 °C; \([\alpha]_{D}^{10} +2.5 (c 1.7, \text{CHCl}_3).\)

MALDI MS: \(m/z [\text{M} + \text{Na}]^+\) calc for C\(_{78}\)H\(_{152}\)O\(_3\)Na: 1174.42; found: 1174.44.

1H NMR (500 MHz, CDCl\(_3\)): \(\delta = 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 \text{ Hz}, 6 \text{ H}), 0.68-0.62 (m, 4 \text{ H}), 0.55 (dt, \(J = 4.1, 8.2 \text{ Hz}, 2 \text{ H}), -0.33 (q, \(J = 4.9 \text{ Hz}, 2 \text{ H}).\)

13C NMR (126 MHz, CDCl\(_3\)): \(\delta = 176.2, 72.3, 51.2, 35.7, 31.9, 30.2, 29.7, 29.65, 29.6, 29.5, 29.4, 29.36, 28.7, 27.4, 25.7, 22.7, 15.8, 14.1, 10.9.\)

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 (0.5 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 aqeous 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; \(\alpha\) 42 (above solvent); \([\alpha]_{D}^{20} +2.5 (c 1.4, \text{CHCl}_3).\)

MS: \(m/z [\text{M} + \text{Na}]^+\) calc for C\(_{78}\)H\(_{152}\)O\(_3\)Na: 1160.1634; found: 1160.1626.

1H NMR (500 MHz, CDCl\(_3\)): \(\delta = 3.73 (td, \(J = 4.8, 7.9 \text{ Hz}, 1 \text{ H}), 2.48 (td, \(J = 5.4, 8.9 \text{ Hz}, 1 \text{ H}), 1.76-1.71 (m, 1 \text{ H}), 1.63-1.60 (m, 2 \text{ H}), 1.54-1.47 (m, 4 \text{ H}), 1.26 (m, 129 H), 0.89 (t, \(J = 6.9 \text{ Hz}, 6 \text{ H}), 0.66-0.62 (m, 4 \text{ H}), 0.57 (dt, \(J = 4.1, 8.2 \text{ Hz}, 2 \text{ H}), -0.33 (q, \(J = 4.9 \text{ Hz}, 2 \text{ H}).\)

13C NMR (126 MHz, CDCl\(_3\)): \(\delta = 178.6, 72.1, 50.8, 36.1, 31.9, 30.2, 29.7, 29.6, 29.5, 29.4, 28.7, 27.3, 25.7, 22.7, 15.8, 14.1, 10.9.\)

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

(R)-2-[(R)-1-Hydroxy-12-[(1\(\alpha\))20]-eicosylcyclopropyl]tetradecyl)cyclopropyl)dodecyl)hexacosanoic Acid (24)

(a) LiHMDS (0.32 mL, 0.24 mmol) was added to a stirred solution of aldehyde 20 (0.17 g, 0.24 mmol) and sultone 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)-(E)]-1-([tert-butylidemethylsilyl]oxy)-2-[(1\(\alpha\)])25]-[24]-[(1\(\alpha\)])25]-2-eicosylocyclopropyl)tetradecyl)cyclopropyl)dodecyl)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-(1-hydroxy-12-((1R)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylthio]-1-phenyl-1H-tetrazole (27).

(a) Diethyl azodicarboxylate (10.6 g, 60.8 mmol) in anhydrous THF (15 mL) was added to a stirred solution of (S)-(1R)-2-(1R,2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropylbutan-1-ol (26) (10.0 g, 46.7 mmol), triphenylphosphine (17.2 g, 65.5 mmol) and 1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-tetrazole (27).

IR: 3317, 2922, 2852, 1681, 1464, 1377, 721 cm⁻¹.

5-((S)-(3-((1R,2R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butan-1-ol 26) (10.0 g, 46.7 mmol), triphenylphosphine (17.2 g, 65.5 mmol) and 1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-tetrazole (27).

IR: 3317, 2922, 2852, 1681, 1464, 1377, 721 cm⁻¹.

5-((S)-(3-((1R,2R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butan-1-ol 26) (10.0 g, 46.7 mmol), triphenylphosphine (17.2 g, 65.5 mmol) and 1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-tetrazole (27).

IR: 3317, 2922, 2852, 1681, 1464, 1377, 721 cm⁻¹.

5-((S)-(3-((1R,2R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butan-1-ol 26) (10.0 g, 46.7 mmol), triphenylphosphine (17.2 g, 65.5 mmol) and 1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-tetrazole (27).

IR: 3317, 2922, 2852, 1681, 1464, 1377, 721 cm⁻¹.

5-((S)-(3-((1R,2R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butan-1-ol 26) (10.0 g, 46.7 mmol), triphenylphosphine (17.2 g, 65.5 mmol) and 1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-tetrazole (27).

IR: 3317, 2922, 2852, 1681, 1464, 1377, 721 cm⁻¹.

5-((S)-(3-((1R,2R)-2-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butan-1-ol 26) (10.0 g, 46.7 mmol), triphenylphosphine (17.2 g, 65.5 mmol) and 1-phenyl-1H-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-((1R,2R)-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl)butylsulfonyl)-1-phenyl-1H-tetrazole (27).

IR: 3317, 2922, 2852, 1681, 1464, 1377, 721 cm⁻¹.
(15Z,2R)-2-octadecylcyclopentyl)[hexa-dec-3-en-2-yl]cyclopentyl)-1,3-dioxolane (4.5 g, 78%) as a colourless oil. Potassium azodicarboxylate (4.5 g, 23.2 mmol) was added to a stirred solution of the above (2.3 g, 11.6 mmol) in anhydrous THF (30 mL) under nitrogen at 10 °C. A solution of glacial acetic acid (3 mL) was added and worked up for 24 h then additional potassium 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 29.

Yield: 2.78 g (73%); colourless oil; [α]D23+4.04 (c 1.46, CHCl3).

MS: m/z [M + Na]+ calc'd for C61H118O2Na: 905.9051; found: 905.9051.

1H NMR (500 MHz, CDCl3): 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), 1.16 (d, J = 6.6 Hz, 3 H), 0.89 (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).

13C NMR (126 MHz, CDCl3): δ = 178.6, 64.4, 38.7, 31.4, 34.4, 31.9, 30.2, 30.0, 29.7, 29.6, 29.5, 29.3, 29.2, 29.2, 28.7, 28.6, 27.2, 27.2, 26.1, 25.9, 25.9, 25.9, 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 (70:20:5 mL). The mixture was stirred at 70 °C for 3 h, then worked up as above to give 16-((15Z,2R)-2-(S)-16-((15Z,2R)-2-Octadecylcyclopentyl)hexadecane-2-yl)cyclopentyl)hexadecan-1-ol.

Yield: 1.5 g (60%); white solid; mp 50–52 °C; [α]D28+3.1 (c 1.1, CHCl3).


1H NMR (500 MHz, CDCl3): 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).

13C NMR (126 MHz, CDCl3): 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, 29.3, 29.2, 28.7, 28.6, 27.2, 27.2, 26.1, 25.9, 25.9, 22.3, 19.6, 18.6, 15.8, 14.0, 10.9, 10.4.

IR: 3419, 2918, 2845, 1471, 1366, 1057, 989, 719 cm⁻¹.

(c) The above alcohol (1.50 g, 19 mmol) was dissolved in hot CH2Cl2 (20 mL) and added to a refluxing stirred suspension of PCC (0.94 g, 4.4 mmol) in CH2Cl2 (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; [α]D24+5.9 (c 1.0, CHCl3).

MS: m/z [M + Na]+ calc'd for C63H130O2Na: 819.8298; found: 819.8280.
Methyl (R)-2-[(1-tert-Butyldimethylsilyloxy)-3-(1-phenyl-1H-tetrazol-5-yl)propyl]hexadecane-2-yl)cyclopropyl)nonadec-4-enyl)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-[(1-tert-butylidimethylsilyloxy)-3-[(1-phenyl-1H-tetrazol-5-yl)propyl]tetracosanoate 35 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-[(1-tert-butylidimethylsilyloxy)-3-[(1-phenyl-1H-tetrazol-5-yl)propyl]tetracosanoate 35 (1.21 g, 1.60 mmol) and methyl (R)-2-[(1-tert-butylidimethylsilyloxy)-3-[(1-phenyl-1H-tetrazol-5-yl)propyl]hexadecane-2-yl)cyclopropyl)nonadec-4-enyl)tetracosanoate. 1H NMR (500 MHz, CDCl3): δ = 3.92–3.89 (m, 1 H), 3.66 (s, 3 H, 2.53 (dd, J = 7.7, 7.2, 11.0 Hz, 1 H), 1.57 (br s, 8 H), 1.37–1.10 (br m, 134 H), 0.48–0.42 (m, 3 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).

IR: 3411, 2919, 2810, 1715, 1618, 1468, 1196, 720 cm–1.

Yield: 0.63 g (70%); white solid; mp 55–56 °C; [α]D22 +5.2 (c 0.50, CHCl3).


(b) Lithium hydroxide monohydrate (0.47 g, 11.2 mmol) was added to a stirred solution of the 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; [α]D22 –0.18 (c 7.2 petrol/EnOAc); [α]D22 +5.2 (c 0.50, CHCl3).

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

(a) Methyl (R)-2-[(1-tert-Butyldimethylsilyloxy)-3-[(1-phenyl-1H-tetrazol-5-yl)propyl]hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoate (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. The organics were washed with brine, dried and evaporated; column chromatography eluting with petroleum/EtOAc (10:1, 70 mL) and neutralised with sat. aq. NaHCO3 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-[(1-Hydroxy-19-((1S,2S)-2-Octadecylcyclopropyl)hexadecane-2-yl)cyclopropyl)nonadecyl)tetracosanoate.

Yield: 0.73 g (72%); white solid; mp 47–48 °C; [α]D22 +8.1 (c 0.19, CHCl3).

IR: 3419, 2917, 2810, 1712, 1618, 1470, 1375, 1197, 719 cm⁻¹.


