

The first syntheses of single enantiomers of the major methoxymycolic acid of *Mycobacterium tuberculosis*

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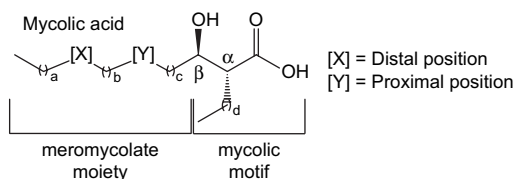
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Abstract—The synthesis of three stereoisomers of a major homologue of the methoxymycolic acids present in *Mycobacterium tuberculosis* is described.

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1. Introduction

Mycolic acids (Scheme 1) are major constituents of the cell envelope of *Mycobacterium tuberculosis* and other mycobacteria, some of which are pathogenic to animals and humans.^{1,2} Their presence is thought to be linked with the resistance of these organisms to most current antibiotics and other chemotherapeutic agents.³ Mycolic acids can be divided into two parts, meromycolate and mycolic motif (Scheme 1). The latter is common to each mycobacterial mycolic acid, except for minor variations in the length of the chain (d).



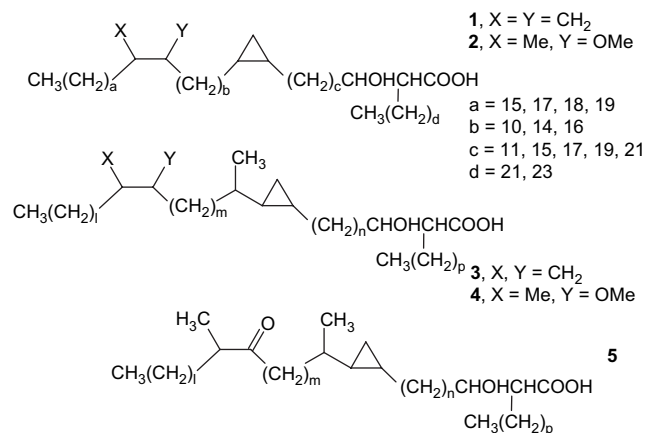
Scheme 1.

The meromycolate moiety, however, is much more variable (Scheme 2), leading to molecules such as α -mycolic acids **1** and **3**, methoxymycolic acids **2** and **4** and ketomycolic acids **5**.^{4,5} The two stereocentres in the α and β -positions relative to the carboxylic group have been found to be both in the *R*-configuration for all the mycolic acids examined, irrespective of the groups in the meromycolate moiety.^{6–10}

Keywords: Methoxymycolic acids; *Mycobacterium tuberculosis*.

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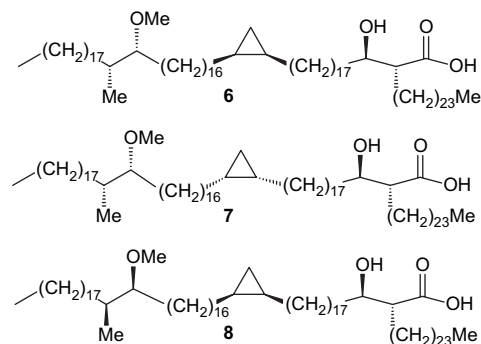
Scheme 2.

The presence of the hydroxyl group and the relative configuration between it and the alkyl chain have been demonstrated to be capable of altering the film molecular packing. The formation of a hydrogen bond between the hydroxyl group and the carboxylic group has a stabilising effect for the aligned conformation between the two long chains.^{11,12} Moreover, the absolute configuration of these two chiral centres is necessary for efficient recognition by T cells and the generation of an immune response by the host organism against pathogenic mycobacteria;¹³ the same is also true for the antitumour properties of mycolic acid derivatives.¹⁴

Mycolic acids are generally present as penta-arabinose tetramycolyl clusters bound to the cell wall or as non-bound species such as trehalose dimycolates (TDMs). These species exert a number of very important immunological effects.¹⁵

Recent studies have indicated that antisera against either *M. tuberculosis* or *Mycobacterium avium* cord factor raised in rabbits preferentially recognise TDM from the species used as antigen source, suggesting that the underlying IgG antibodies were directed at the specific mycolic acids rather than the common sugar backbone.^{16,17} Moreover, in a key paper, it was reported that the reactivity of human antisera to various mycolic acid subclasses is different, anti-cord factor IgG antibody recognising methoxymycolic acids more strongly than keto- or α -mycolic acids.^{18,16} Moreover, α -mycolates stimulate DN1/JRT3 cells at least 100 times less than methoxy or ketomycolates.¹⁹ The biosynthesis of keto- and methoxymycolates is closely linked through a common hydroxymycolate precursor, that is, the product of the MMAS-4 enzyme.^{2,20–22} Structural variations in the meromycolate chain may be of crucial biological importance because mutants without some groups profoundly alter membrane permeability and affect virulence.^{21–24} *Mycobacterium marinum* is an established model for discovering genes involved in mycobacterial infection; kasB mutants synthesise mycolic acids, which, among other changes, show a significant reduction in ketomycolate content and a small increase in α - and methoxymycolates. These show markedly different cell wall permeability and a marked increase in susceptibility to lipophilic antibiotics.²⁵ These results suggest that methoxymycolic acids may play a particular role in the pathogenesis of *M. tuberculosis*.

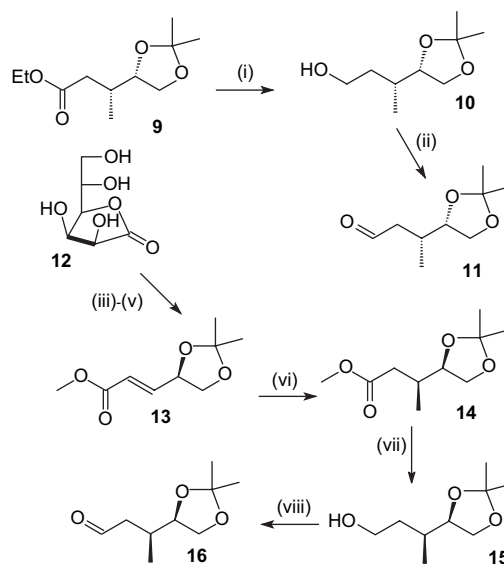
In one strain of *M. tuberculosis*, the methyl and methoxy fragments have been shown to be of *S,S*-configuration on the basis of the additivity of optical rotations.^{7,20,6} The methyl branch of wax esters apparently derived by enzymatic oxidation of ketomycolic acids is also of *S*-stereochemistry.⁴³ Other reports identify a *R*-stereochemistry for the three stereocentres of the α -methyl-*trans*-epoxy unit in related mycolic acids.⁸ Little is known about the absolute stereochemistry of the *cis*-cyclopropane. Interestingly, however, a recent computational study of the binding of a model methoxymycolic acid glucose ester to the human MHC class I like molecule CD1b using a *R,R*-configuration for the α -methyl- β -methoxy unit shows a close fit to the shape of a non-functional natural mycolate.²⁶ The same paper reports a similar good fit for a model α -mycolic acid having a distal cyclopropane with an *S,R*-configuration. Other crystal structures give indications of the nature and geometry of the active site in related enzymes,^{27–29} with no modelling of bound mycolates. A further study³⁰ is reported to show the fit of a putative α -mycolate containing a distal α -methyl-*trans*-cyclopropane and a proximal *cis*-cyclopropane to the CD1 receptor, but the actual fit appears to be with a structure having the methyl group one carbon removed from the *trans*-cyclopropane and with the second cyclopropane having *trans*-geometry. We have reported the synthesis of single enantiomers of the major α -mycolic acid of *M. tuberculosis*,³¹ of related meromycolates³² and of wax esters containing an α -methyl-*trans*-cyclopropane fragment.^{33,34} We now report the first syntheses of three stereoisomers of a complete methoxymycolic acid (Scheme 3) corresponding to the major component of this type isolated from *M. tuberculosis*,^{4,6} in order that the role of these acids and of their stereoisomers may be determined.



Scheme 3.

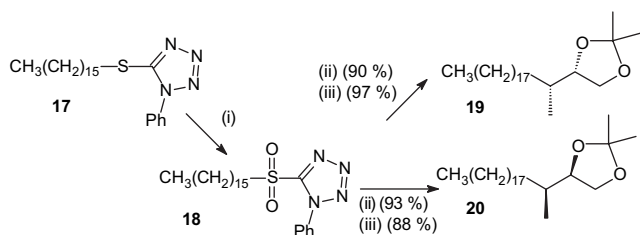
2. Results and discussion

The α -methyl- β -methoxy unit was first prepared from manitol by a known sequence leading to the aldehyde **11**.^{35,36} In a similar way, the enantiomer **16** was prepared from L-gulono-1,4-lactone (**12**), derived by hydrogenation of ascorbic acid.³⁷ In a modification of the literature procedure,³⁸ the lactone was protected as the acetal with 2-methoxypropene, oxidatively cleaved with sodium periodate and then reacted with methyl diisopropoxyphosphinyl acetate and potassium carbonate to give the ester **13** in 34% overall yield in a one-pot process.^{37,38} This gave the *E*-alkene rather than an *E/Z* mixture as described earlier. The ester was treated with methyl lithium as in the preparation of the enantiomer **9** to give **14**; this was in turn converted into the enantiomeric aldehyde **16** (Scheme 4).



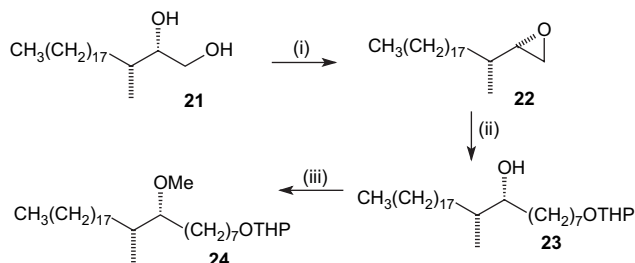
Scheme 4. (i) LiAlH₄, THF (96%); (ii) PCC (80%); (iii) pyridinium *p*-toluene sulfonate, 2-methoxypropene, DMF; (iv) NaIO₄; (v) methyl diisopropoxyphosphinyl acetate, K₂CO₃ (34%, three steps); (vi) MeLi, –78 °C (82%); (vii) LiAlH₄, THF (80%); (viii) PCC (81%).

The aldehydes were each then homologated to **19** and **20**, respectively, by reaction with the sulfone **18** and base in a modified Julia–Kocienski reaction, followed by hydrogenation of the *E/Z* mixtures of alkenes produced. Sulfone **18** was in turn prepared by reaction of 1-phenyl-1*H*-tetrazole-5-thiol with 1-bromohexadecane to give **17**, followed by oxidation (Scheme 5).



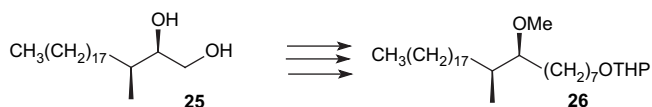
Scheme 5. (i) H_2O_2 , $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$, IMS (93%); (ii) LiHMDS, **16** (for **20**) or **11** (for **19**); (iii) H_2 , Pd/C.

Each acetal was deprotected to the corresponding diol, e.g., **21**, which was in turn converted into the epoxide **22** via the monotosylate. The epoxide was opened to form alcohol **23** by reaction with the Grignard reagent prepared from 6-bromotetrahydropyranoloxhexane (Scheme 6).



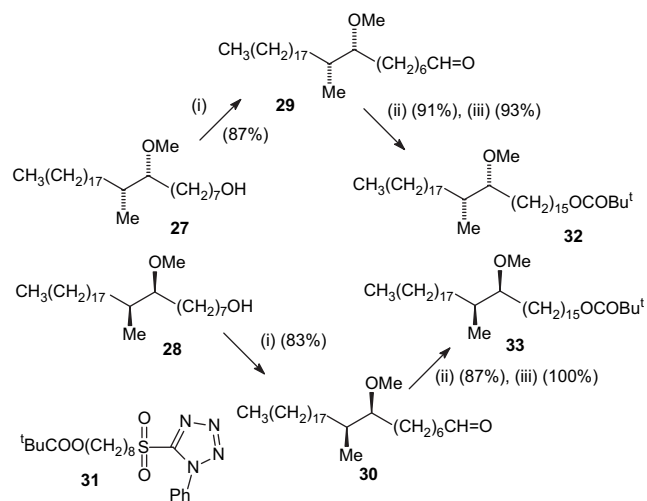
Scheme 6. (i) NaOH, cetrimide, *p*TsCl, CH_2Cl_2 (97%); (ii) $\text{BrMg}(\text{CH}_2)_6\text{OTHP}$, CuI, THF (75%); (iii) NaH, THF, MeI (94%).

Methylation of the alcohol **23** led to **24** containing the required relative stereochemistry of the branch methyl and methoxy groups. In the same way, the diol **25** was converted into **26** (Scheme 7).



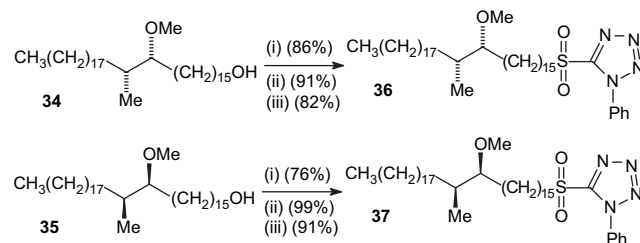
Scheme 7.

Deprotection of the acetals **24** and **26** to alcohols **27** and **28** followed by oxidation and homologation, again using a modified Julia–Kocienski reaction with **31**, then hydrogenation, generated the esters **32** and **33** (Scheme 8).



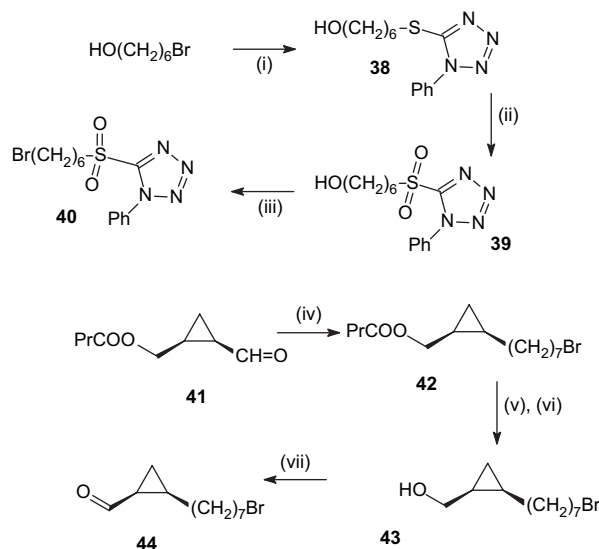
Scheme 8. (i) PCC; (ii) **31**, LiHMDS; (iii) H_2 , Pd/C.

The esters **32** and **33** were deprotected to the primary alcohols **34** and **35**, converted into the bromides and hence, via the corresponding sulfides, to sulfones **36** and **37** (Scheme 9).



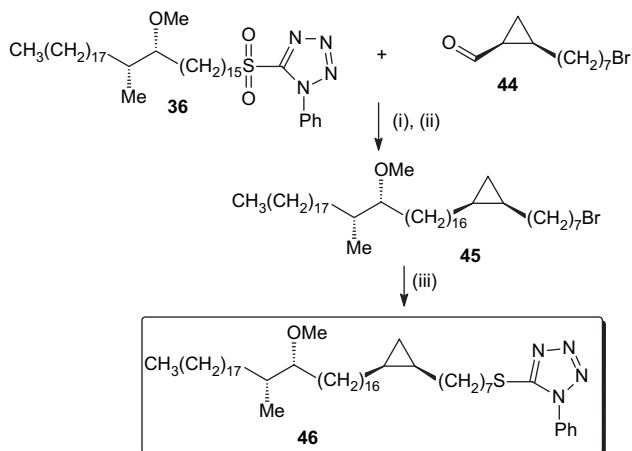
Scheme 9. (i) *N*-Bromosuccinimide, PPh_3 , CH_2Cl_2 ; (ii) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 ; (iii) H_2O_2 , $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$, IMS.

The sulfones were then treated with a single enantiomer of cyclopropane aldehyde, prepared as described below. The aldehyde **41** was prepared by standard methods.³⁹ Reaction with the sulfone **40** (prepared as shown) and base in a modified Julia–Kocienski reaction, followed by hydrogenation of the derived *E/Z*-alkenes gave the ester **42**, which was transformed routinely into **44** (Scheme 10).



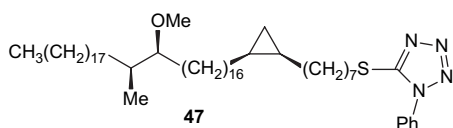
Scheme 10. (i) 1-Phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (99.5%); (ii) H_2O_2 , $\text{Mo}_7\text{O}_{24}(\text{NH}_4)_6 \cdot 4\text{H}_2\text{O}$, IMS (90%); (iii) *N*-bromosuccinimide, PPh_3 (86%); (iv) LiHMDS, THF, **40** (78%); (v) 2,4,6-triisopropylbenzene sulfonylhydrazide, THF (67%); (vi) K_2CO_3 , MeOH (84%); (vii) PCC (93%).

A further Julia reaction of **44** with sulfone **36**, followed by hydrogenation generated the bromide **45** containing both the functionalities of the methoxymycolic acid, which was further converted into sulfide **46** (Scheme 11).



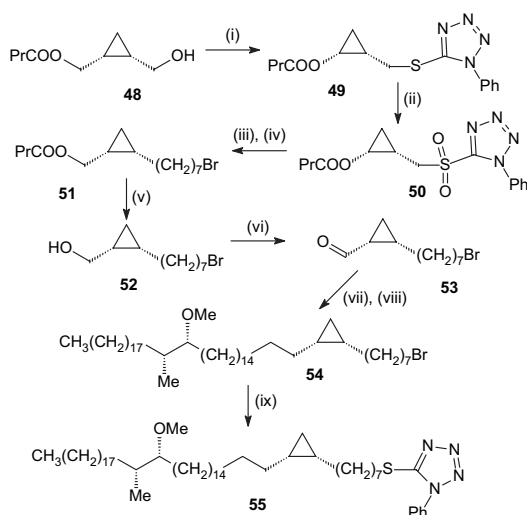
Scheme 11. (i) LiHMDS, THF (92%); (ii) triisopropylbenzene sulfonylhydrazide, THF (91%); (iii) 1-phenyl-1*H*-tetrazol-5-thiol, K₂CO₃ (91%).

By repeating this process with sulfone **37**, the isomeric sulfide **47** was obtained (Scheme 12).



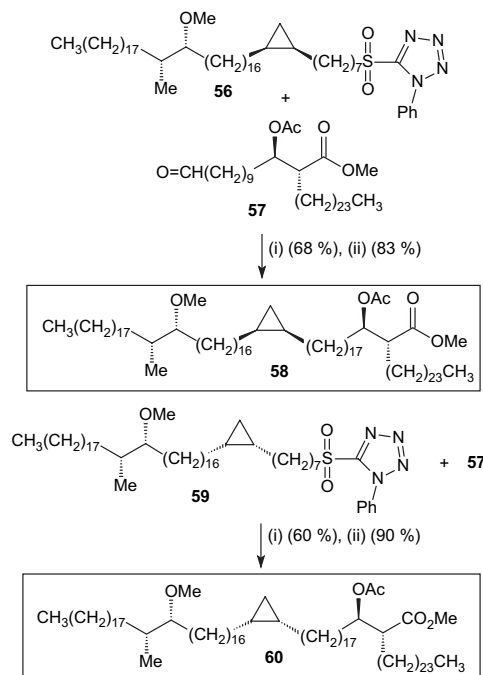
Scheme 12.

The analogous intermediates with the opposite cyclopropane stereochemistry could be prepared in a similar way. The known cyclopropane **48**³⁹ was converted into the thioether **49** by reaction with diethyl azodicarboxylate, triphenylphosphine and 1-phenyl-1*H*-tetrazol-5-thiol. This in turn was oxidised to the corresponding sulfone **50** and chain extended as before to produce bromide **51**. Removal of the ester protecting group, oxidation and a Julia reaction followed by hydrogenation led to the required bromide **54**. This was further converted into the sulfide **55** as before (Scheme 13).



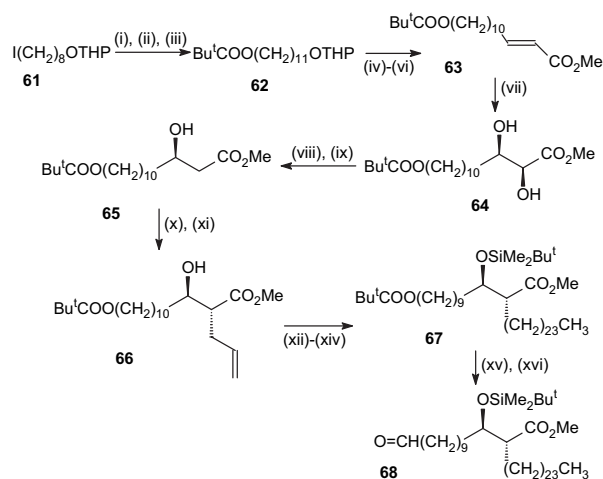
Scheme 13. (i) Diethyl azodicarboxylate, 1-phenyl-1*H*-tetrazol-5-thiol, PPh₃, THF (85%); (ii) H₂O₂, Mo₇O₂₄(NH₄)₆·4H₂O, IMS (93%); (iii) LiHMDS, THF, 6-bromohexanal (74%); (iv) 2,4,6-triisopropyl sulfonylhydrazide, THF (80%); (v) K₂CO₃, MeOH (85%); (vi) PCC (76%); (vii) LiHMDS, **36**, THF (74%); (viii) 2,4,6-triisopropyl sulfonylhydrazide, THF (80%); (ix) 1-phenyl-1*H*-tetrazol-5-thiol, K₂CO₃ (88%).

The final stage of the syntheses required the oxidation of each of the sulfides **46**, **47** and **55** to the corresponding sulfones and coupling of each to a unit containing the pre-formed protected hydroxy acid of the mycolate motif (Scheme 1). This was introduced in the cases of **56** and **59**, derived from **46** and **55**, respectively (Scheme 14), using the aldehyde **57**, the synthesis of which was reported earlier.³¹



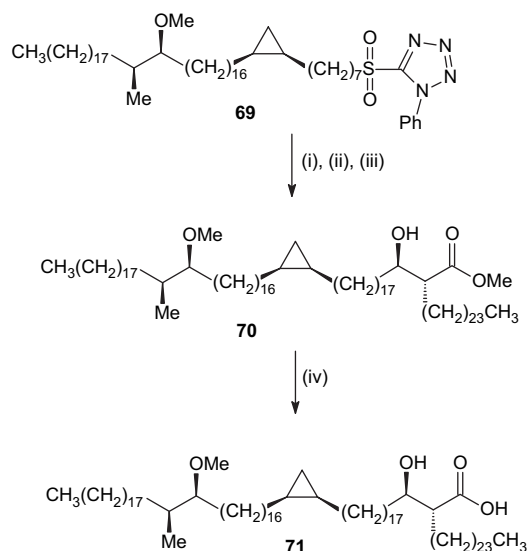
Scheme 14. LiHMDS, THF; (ii) KOOCCN=NCOOK, AcOH, MeOH, THF.

In the cases of the sulfone derived from **47**, a modified aldehyde **68** was used, prepared using a more efficient method, and with a silyl protecting group that proved to be easier to remove selectively. The aldehyde was prepared as shown in Scheme 15.⁴²



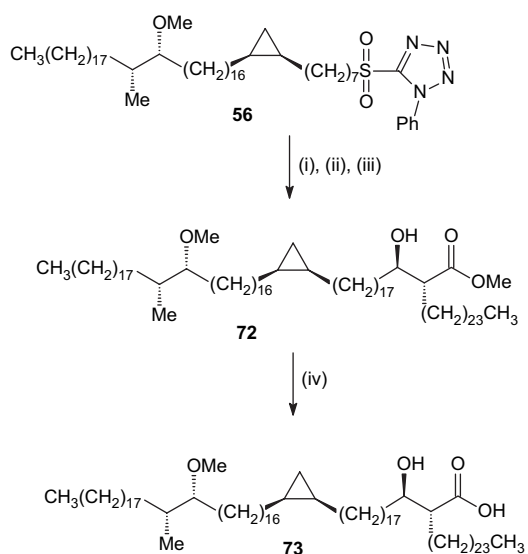
Scheme 15. (i) Li, NH₃, prop-2-yn-1-ol (94%); (ii) NaBH₄, Ni(OAc)₂, EtOH, H₂ (83%); (iii) pivaloyl chloride, Et₃N, DMAP (91%); (iv) *p*TsOH, MeOH, THF (89%); (v) PCC (8%); (vi) Ph₃PCHCO₂Me, toluene (85%); (vii) (DHQD)₂-PHAL, K₃Fe(CN)₆, K₂CO₃, OsO₄, MeSO₂NH₂, Bu^tOH, H₂O (97%); (viii) SOCl₂, CCl₄, NaIO₄, RuCl₃·H₂O (93%); (ix) NaBH₄, DMAC, THF, H₂O, H₂SO₄ (68%); (x) LDA, allyl iodide, HMPA (55%); (xi) imidazole, DMF, TBDMSCl (91%); (xii) OsO₄, lutidine, NaIO₄, dioxane, H₂O (93%); (xiii) LiHMDS, 5-docosan-1-sulfonyl-1-phenyl-1*H*-tetrazole (83%); (xiv) H₂, Pd/C (87%); (xv) KOH, THF, MeOH, H₂O (80%); (xvi) PCC (84%).

Reaction of the aldehyde **68** with sulfone **69**, derived from **47**, in the presence of lithium hexamethyldisilazide, followed by saturation of the double bond and removal of the silyl group led to the methyl ester of the corresponding methoxymycolic acid, **70**. This could be converted into the free acid **71** by reaction with lithium hydroxide in THF/MeOH/water (Scheme 16).



Scheme 16. (i) LiHMDS, THF, **68** (80%); (ii) KOOCN=NCOOK, AcOH/MeOH, THF (85%); (iii) HF, pyridine, THF (83%); (iv) LiOH, THF, MeOH, H₂O (66%).

In the same way reaction of the aldehyde **68** with sulfone **56** led to the corresponding methoxymycolic acid either protected as its methyl ester **72** or unprotected **73** (Scheme 17).



Scheme 17. (i) LiHMDS, THF, **68** (77%); (ii) KOOCN=NCOOK, AcOH/MeOH, THF (81%); (iii) HF, pyridine, THF (84%); (iv) LiOH, THF, MeOH, H₂O (63%).

The proton and carbon NMR spectra of **58** and **60** were essentially identical. The proton and carbon NMR spectra of the synthetic hydroxy esters **70** and **72** were identical to each other and to those of a natural sample. The MALDI

mass spectrum of **70** showed a molecular isotope ion pattern starting at 1290 that corresponded to that for the major component of the natural sample. The specific rotations provided rather more insight into which of them corresponded to the natural component. Thus the natural sample of the methyl ester showed an $[\alpha]_D^{22}$ of -0.83 (the literature value reported in 1966 was -0.1).⁶ Compounds **58** and **60** showed $[\alpha]_D^{22}$ $+7.2$ and $+7.7$, respectively, while the hydroxy esters **72** and **73** gave $[\alpha]_D^{22}$ $+6.0$ and $+7.0$, respectively. In contrast **70** and **71** gave -1.0 and -1.1 , respectively. The specific rotations of these molecules are determined very largely by the hydroxy acid and methoxy methyl fragment stereochemistries and are affected to only a very small degree by the stereochemistry of the *cis*-cyclopropane. It seems extremely likely, therefore, that the methoxy methyl fragment is of *S,S*-stereochemistry. The fourth possible stereoisomer is readily available by simple modification of the routes described above. Currently, the biological properties of the synthetic methoxymycolic acids are being determined in order to establish firmly whether the stereochemistry is critical to biochemical effect and to establish the absolute stereochemistry present in the natural material.

3. Experimental section

3.1. General

Chemicals used were obtained from commercial suppliers or prepared from them by methods described. Solvents, which had to be dry, e.g., ether and tetrahydrofuran were dried over sodium wire. Petrol was of boiling point 40–60 °C. Reactions carried under inert conditions were carried out under a slow stream of nitrogen. Those carried out at low temperatures were cooled using a bath of methylated spirit with liquid nitrogen. Silica gel (Merck 7736) and silica plates used for column and thin layer chromatographies were obtained from Aldrich. Organic solutions were dried over anhydrous magnesium sulfate. GLC was carried out on a Perkin–Elmer Model 8410 on a capillary column (15 m × 0.53 mm). IR spectra were carried out on a Perkin–Elmer 1600 FTIR spectrometer as liquid films. NMR spectra were recorded on a Bruker AC250 or Advance 500 spectrometer. Where signs are given in carbon spectra, $+$ = CH₂, $-$ = CH, CH₃ and no sign is quaternary; in some molecules containing long carbon chains, it was not possible to identify a signal for each individual carbon. $[\alpha]_D$ values were recorded in CHCl₃ on a POLAAR 2001 Optical Activity polarimeter. Mass spectra were recorded on a Bruker MicroTOF.

3.1.1. (*E*)-3-((*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl)acrylic acid methyl ester (13**).** Pyridinium-*p*-toluene sulfonate (1.76 g, 7.02 mmol) was added to a stirred solution of L-gulono-1,4-lactone (**12**) (25 g, 140 mmol)³⁷ in anhydrous formamide (200 mL) at 10 °C, followed by dropwise addition of 2-methoxypropene (13.14 g, 182.5 mmol). The cooling bath was removed and the reaction mixture was stirred for 6 h, when TLC showed one spot. Sodium carbonate decahydrate (30 g) was added, the suspension was stirred vigorously for 2 h and then filtered over Celite. The filtrate was evaporated at 50–40 °C and 0.1–0.2 mm Hg. The residue was stirred in water (200 mL), then sodium metaperiodate (60.1 g, 280 mmol) was added in small portions at

0–5 °C, whilst maintaining the pH at 5.5 by the addition of 2 N sodium hydroxide. After stirring at room temperature for 2 h, sodium chloride (30 g) was added. The precipitate was filtered and washed with water (100 mL). The filtrate was diluted with 10% sodium hydrogen carbonate (150 mL) followed by the addition of methyl diisopropoxyphosphinyl acetate (36.7 g, 154.3 mmol) and then 6 M aq potassium carbonate (130 mL) at 5 °C. The mixture was stirred for 16 h at room temperature and then extracted with dichloromethane (3×200 mL). The combined organic layers were washed with brine, water, dried and evaporated to give a pale yellow oil. Chromatography on silica eluting with 5:2 petrol/ether gave (*E*)-3-((*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)acrylic acid methyl ester (**13**) (9.00 g, 34.3%) $\{[\alpha]_{\text{D}}^{22} -42.9$ (*c* 1.25, CHCl₃); lit.:³⁸ $[\alpha]_{\text{D}}^{20} -46$ (*c* 1, CHCl₃)}, which showed δ_{H} (500 MHz, CDCl₃): 6.88 (1H, dd, *J* 5.7, 15.8 Hz), 6.10 (1H, dd, *J* 1.3, 15.8 Hz), 4.66 (1H, br dq, *J* ca. 1.5, 6.9 Hz), 4.18 (1H, dd, *J* 6.7, 8.2 Hz), 3.74 (3H, s), 3.67 (1H, dd, *J* 7.0, 8.2 Hz), 1.44 (3H, s), 1.40 (3H, s); δ_{C} (125 MHz, CDCl₃): 166.4, 145.0, 121.9, 110.2, 74.9, 68.8, 51.7, 26.4, 25.7.

3.1.2. (*R*)-3-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)butyric acid ethyl ester (9**).** Methylolithium (54 mL, 80 mmol, 1.5 M) was added to a stirred solution of ethyl *E*-3-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)acrylate (8 g, 40 mmol) in dry ether (250 mL) at –78 °C under nitrogen, stirred at this temperature for 2.5 h and then allowed to reach –60 °C followed by the addition of water (10 mL). After 5 min, satd aq ammonium chloride (60 mL) was added, whereupon the temperature rose to –40 °C. The mixture was allowed to reach 0 °C and quenched with water (100 mL). The organic layer was separated and the aqueous layer extracted with ether (2×50 mL). The combined layers were washed with satd aq sodium chloride (2×100 mL) dried and evaporated to give a yellow oil, which was purified by chromatography on silica eluting with petrol/ether (8:2) (TLC visualised with potassium permanganate) to give (*R*)-3-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)butyric acid ethyl ester (**9**) as a colourless oil (7.27 g, 84%)³⁵ $\{[\alpha]_{\text{D}}^{22} +8.34$ (*c* 1.12, CHCl₃)}, which showed δ_{H} (500 MHz, CDCl₃): 4.07 (2H, q, *J* 7.0 Hz), 3.97–3.91 (2H, m), 3.57 (1H, br t, *J* 6.7 Hz), 2.33 (1H, br dd, *J* 4.5, 14.9 Hz), 2.18–2.11 (1H, m), 2.07 (1H, br dd, *J* 8.9, 14.9 Hz), 1.34 (3H, s), 1.27 (3H, s), 1.20 (3H, t, *J* 7.0 Hz), 0.94 (3H, d, *J* 7.0 Hz); δ_{C} (125 MHz, CDCl₃): 172.5, 108.8, 78.7, 66.7, 60.3, 37.5, 32.9, 26.3, 25.2, 15.3, 14.1; ν_{max} : 2984, 2980, 1732, 1012 cm^{–1}. A small amount of what was probably a stereoisomer was also isolated (0.9 g).

3.1.3. (*S*)-3-((*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl)butyric acid methyl ester (14**).** Methylolithium (68 mL, 102 mmol, 1.5 M) was added to a stirred solution of (*E*)-3-((*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)acrylic acid methyl ester (**13**) (9.31 g, 50 mmol) in ether (250 mL) at –78 °C under nitrogen. The mixture was stirred at this temperature for 2.5 h and then allowed to reach –60 °C followed by the addition of water (10 mL). After 5 min, satd aq ammonium chloride (60 mL) was added, whereupon the temperature rose to –40 °C. Work up as above gave (*S*)-3-((*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)butyric acid methyl ester (**14**) (7.64 g, 82%) $\{[\alpha]_{\text{D}}^{22} -8.16$ (*c* 1.47, CHCl₃)}, which showed δ_{H} (500 MHz, CDCl₃): 4.02 (1H, br q, *J* 6.3 Hz), 3.99 (1H, br q, *J* 6.6 Hz), 3.67 (3H, s), 3.61 (1H, br t, *J* 7.0 Hz), 2.42

(1H, dd, *J* 4.8, 14.9 Hz), 2.24–2.18 (1H, m), 2.16 (1H, dd, *J* 8.9, 14.9 Hz), 1.39 (3H, s), 1.33 (3H, s), 0.99 (3H, d, *J* 6.6 Hz); δ_{C} (125 MHz, CDCl₃): 173.1, 108.9, 78.7, 66.7, 51.5, 37.3, 32.9, 26.3, 25.2, 15.3; ν_{max} : 2985, 1740, 1065 cm^{–1}.

3.1.4. (*R*)-3-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)butan-1-ol (10**).** (*R*)-3-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)butyric acid ethyl ester (**9**) (10.8 g, 50 mmol) in tetrahydrofuran (40 mL) was added dropwise over 15 min to a suspension of lithium aluminium hydride (2 g, 53 mmol) in tetrahydrofuran (160 mL) at room temperature. The mixture was refluxed for 1 h, when TLC showed that no starting material was left, then cooled to room temperature and quenched carefully with freshly prepared satd aq sodium sulfate decahydrate (10 mL) until a white precipitate was formed, followed by the addition of magnesium sulfate (10 g). The mixture was stirred vigorously for 10 min and then filtered through a pad of Celite and washed well with tetrahydrofuran (2×50 mL). The combined organic layers were evaporated to give a residue, which was dissolved in 1:1 petrol/ether (150 mL) and two drops of triethylamine. The solution was dried by stirring for 1 h over anhydrous potassium carbonate. Filtration and evaporation gave a colourless liquid, (*R*)-3-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)butan-1-ol (**10**)³⁶ (8.4 g, 96%) $\{[\alpha]_{\text{D}}^{22} +18.1$ (*c* 1.35, CHCl₃); lit.:⁴⁰ $[\alpha]_{\text{D}}^{22} +16.8$ (CHCl₃)}, which showed δ_{H} (500 MHz, CDCl₃): 4.01–3.96 (2H, m), 3.75–3.70 (1H, m), 3.66–3.60 (2H, m), 2.06 (1H, t, *J* 5.1 Hz), 1.86–1.78 (1H, m), 1.67–1.61 (1H, m), 1.44–1.37 (4H, including a 3H-singlet at 1.40), 1.34 (3H, s), 0.97 (3H, d, *J* 6.6 Hz); δ_{C} (125 MHz, CDCl₃): 108.7, 79.6, 67.2, 60.3, 35.6, 32.8, 26.4, 25.3, 15.1; ν_{max} : 3424 cm^{–1}.

3.1.5. (*S*)-3-((*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl)butan-1-ol (15**).** (*S*)-3-((*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl)butyric acid methyl ester (**14**) (11.23 g, 60.0 mmol) in tetrahydrofuran (60 mL) was added as above to a suspension of lithium aluminium hydride (2.8 g, 73.8 mmol) in tetrahydrofuran (200 mL). The mixture was refluxed for 1 h and then worked up as above to give (*S*)-3-((*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)butan-1-ol (**15**) (8.4 g, 80%) $\{[\alpha]_{\text{D}}^{22} -18.64$ (*c* 1.15, CHCl₃)}, which showed an identical NMR spectrum to that above.

3.1.6. (*R*)-3-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)-butyraldehyde (11**).** (*R*)-3-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)butan-1-ol (**10**) (6.1 g, 35 mmol) in dichloromethane (30 mL) was added to a stirred suspension of pyridinium chlorochromate (16 g, 92 mmol) in dichloromethane (250 mL) at room temperature. The mixture was stirred vigorously and refluxed for 30 min, when TLC showed that no starting material was left. It was cooled, poured into ether (200 mL) and filtered through a pad of silica, then washed well with ether and the filtrate was evaporated to give a residue. Chromatography on silica eluting with 1:1 petrol/ether gave (*R*)-3-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-butyraldehyde (**11**)³⁶ as a colourless oil (4.82 g, 80%) $\{[\alpha]_{\text{D}}^{22} +8.27$ (*c* 1.44, CHCl₃)}, which showed δ_{H} (500 MHz, CDCl₃): 9.72 (1H, t, *J* 1.9 Hz), 4.03 (1H, br td, *J* 5.1, 6.6 Hz), 3.93 (1H, dd, *J* 6.6, 8.2 Hz), 3.58 (1H, dd, *J* 7.0, 8.2 Hz), 2.51 (1H, ddd, *J* 1.9, 5.4, 16.6 Hz), 2.36–2.29 (1H, m), 2.25 (1H, ddd, *J* 2.2, 7.9, 16.6 Hz), 1.35 (3H, s),

1.29 (3H, s), 0.95 (3H, d, J 6.9 Hz); δ_C (125 MHz, $CDCl_3$): 201.5, 108.9, 78.4, 66.1, 46.4, 30.3, 26.1, 25.0, 15.4; ν_{max} : 2985, 1725, 1215, 1066 cm^{-1} .

3.1.7. (S)-3-((R)-2,2-Dimethyl[1,3]dioxolan-4-yl)-butyraldehyde (16). (S)-3-((R)-2,2-Dimethyl[1,3]dioxolan-4-yl)-butan-1-ol (**15**) (6.79 g, 39 mmol) in dichloromethane (40 mL) was added to a stirred suspension of pyridinium chlorochromate (16.8 g, 78 mmol) in dichloromethane (250 mL) at room temperature. The mixture was stirred vigorously and refluxed for 30 min; work up as above gave (S)-3-((R)-2,2-dimethyl[1,3]dioxolan-4-yl)butyraldehyde (**16**) as a colourless oil (5.42 g, 81%) $\{[\alpha]_D^{22} -8.6$ (c 1.035, $CHCl_3$), which showed an identical NMR spectrum to that above.

3.1.8. 5-Hexadecylsulfanyl-1-phenyl-1H-tetrazole (17). 1-Bromohexadecane (16.2 g, 53 mmol) was added with vigorous stirring to 1-phenyl-1H-tetrazole-5-thiol (8.4 g, 47 mmol) and anhydrous potassium carbonate (15.2 g, 110 mmol) in acetone (165 mL). The mixture was refluxed for 2.5 h when TLC showed that no starting material was left. The inorganic salts were filtered off and washed with acetone; the solution was evaporated to a small bulk and the residue extracted between dichloromethane (150 mL) and water (300 mL). The aqueous layer was extracted with dichloromethane (2×50 mL). The combined organic phases were washed with water (300 mL), dried and evaporated to give a solid. This was dissolved in acetone (50 mL) and diluted with methanol (100 mL), and left at ambient temperature for 1 h and then at 0 °C for 1 h. The crystals were filtered off and washed with cold 1:2 acetone/methanol to yield a white solid, 5-hexadecylsulfanyl-1-phenyl-1H-tetrazole (**17**) (18 g, 95%). [Found $[M+H]^+$: 403.2876. $C_{23}H_{39}N_4S$ requires: 403.2889. Found: C, 69.0; H, 9.7; N, 14.2. $C_{23}H_{38}N_4S$ requires: C, 68.61; H, 9.51; N, 13.91.] Mp 48–50 °C; δ_H (500 MHz, $CDCl_3$): 7.59–7.52 (5H, m), 3.39 (2H, t, J 7.6 Hz), 1.82 (2H, pent, J 7.6 Hz), 1.43 (2H, pent, J 6.6 Hz), 1.33–1.24 (24H, m), 0.88 (3H, t, J 6.9 Hz); δ_C (125 MHz, $CDCl_3$): 154.5, 133.8, 130.0(–), 129.7(–), 123.8(–), 33.4(+), 31.9(+), 29.63(+), 29.62(+), 29.60(+), 29.56(+), 29.50(+), 29.4(+), 29.3(+), 29.1(+), 29.0(+), 28.6(+), 22.6(+), 14.0(–); ν_{max} : 2917, 1501, 1091, 759 cm^{-1} .

3.1.9. 5-(Hexadecane-1-sulfonyl)-1-phenyl-1H-tetrazole (18). A solution of ammonium molybdate(VI) tetrahydrate (23.7 g, 19.2 mmol) in ice cold H_2O_2 (35% w/w, 53 mL) was added to a stirred solution of 5-hexadecylsulfanyl-1-phenyl-1H-tetrazole (**17**) (17 g, 42.2 mmol) in THF (180 mL) and IMS (360 mL) at 12 °C and stirred at 15–20 °C for 2 h. A further solution of ammonium molybdate(VI) tetrahydrate (9 g, 7.3 mmol) in ice cold H_2O_2 (35% w/w, 23 mL) was added and the mixture was stirred at room temperature for 18 h, then poured into 3 L of water and extracted with dichloromethane (3×200 mL). The combined organic phases were washed with water (2×300 mL), dried and evaporated. The residue was dissolved in methanol (200 mL) and left at ambient temperature for 1 h and then at 0 °C for 1 h. A white solid crystallised; this was filtered and washed with cold methanol to give 5-(hexadecane-1-sulfonyl)-1-phenyl-1H-tetrazole (**18**) (16.97 g, 93%), mp 65–67 °C. [Found $[M+H]^+$: 457.2649. $C_{23}H_{38}N_4SO_2Na$

requires: 457.2608. Found: C, 63.6; H, 9.0; N, 12.7. $C_{23}H_{38}N_4O_2S$ requires: C, 63.56; H, 8.81; N, 12.89.] δ_H (500 MHz, $CDCl_3$): 7.72–7.68 (2H, m), 7.64–7.58 (3H, m), 3.73 (2H, distorted t, J 7.9 Hz), 1.95 (2H, pent, J 7.0 Hz), 1.50 (2H, pent, J 7.0 Hz), 1.36–1.25 (24H, br m), 0.89 (3H, t, J 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 153.5, 133.1, 131.5(–), 129.7(–), 125.1(–), 57.0(+), 31.9(+), 29.7(+), 29.67(+), 29.64(+), 29.6(+), 29.5(+), 29.4(+), 29.2(+), 28.9(+), 22.7(+), 22.0(+), 14.1(–); ν_{max} : 2918, 1470, 1343, 1154, 770 cm^{-1} .

3.1.10. (S)-2,2-Dimethyl-4-((R)-1-methylnonadecyl)-[1,3]dioxolane (19). Lithium hexamethyldisilazide (34 mL, 36 mmol, 1.06 M) was added dropwise with stirring to (R)-3-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)-butyraldehyde (**11**) (3.3 g, 19.6 mmol) and 5-(hexadecane-1-sulfonyl)-1-phenyl-1H-tetrazole (**18**) (10.5 g, 24.1 mmol) in dry tetrahydrofuran (130 mL) under nitrogen at –2 °C. The mixture was allowed to reach room temperature and stirred for 16 h and then quenched with water (100 mL) and petrol/ether (1:1, 100 mL). The aqueous layer was re-extracted with petrol/ether (1:1, 2×50 mL). The combined organic layers were washed with satd aq sodium chloride (2×100 mL), dried and evaporated to give a thick oil. Chromatography on silica eluting with petrol/ether (10:0.5) gave (S)-2,2-dimethyl-4-((E,Z)-(R)-1-methylnonadec-3-enyl)-[1,3]dioxolane (6.5 g, 90%) (2.6:1, E/Z). Palladium on charcoal (10%, 1 g) was added to a stirred solution of the alkenes (6.5 g, 17 mmol) in ethanol (100 mL) and methanol (25 mL). The mixture was stirred under hydrogen at atmospheric pressure. When no more hydrogen was absorbed it was filtered through Celite and washed with warm ethyl acetate (100 mL). The clear colourless filtrate was evaporated at 14 mm Hg to give (S)-2,2-dimethyl-4-((R)-1-methylnonadecyl)-[1,3]dioxolane (**19**) as a white solid (6.3 g, 97%), mp 34–36 °C [found $[M-H]^+$: 381.3723; $C_{25}H_{49}O_2$ requires: 381.3733] $\{[\alpha]_D^{22} +23$ (c 0.62, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.00 (1H, dd, J 6.0, 7.6 Hz), 3.87 (1H, br q, J 7.2 Hz), 3.61 (1H, br t, J 7.6 Hz), 1.61–1.54 (1H, m), 1.41 (3H, s), 1.36 (3H, s), 1.33–1.21 (33H, br s), 1.12–1.05 (1H, m), 0.97 (3H, d, J 6.6 Hz), 0.89 (3H, t, J 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 108.5, 80.4, 67.8, 36.5, 32.8, 31.9, 29.9, 29.70, 29.67, 29.6, 29.4, 27.0, 26.6, 25.5, 22.7, 15.6, 14.1; ν_{max} : 2919, 2851, 1467, 1076, 856 cm^{-1} (see also Supplementary data).

3.1.11. (R)-2,2-Dimethyl-4-((S)-1-methylnonadecyl)-[1,3]dioxolane (20). Lithium hexamethyldisilazide (40 mL, 41 mmol, 1.06 M) was added dropwise to a stirred solution of (S)-3-((R)-2,2-dimethyl[1,3]dioxolan-4-yl)-butyraldehyde (**16**) (5.6 g, 32.5 mmol) and 5-(hexadecane-1-sulfonyl)-1-phenyl-1H-tetrazole (**18**) (14.5 g, 33.36 mmol) in dry tetrahydrofuran (200 mL) under nitrogen at –2 °C. The mixture was allowed to reach room temperature and stirred for 16 h and then worked as above to give (R)-2,2-dimethyl-4-((E,Z)-(S)-1-methylnonadec-3-enyl)-[1,3]dioxolane (11.5 g, 93%) (2.4:1, E/Z), which was hydrogenated and purified as before to give (R)-2,2-dimethyl-4-((S)-1-methylnonadecyl)-[1,3]dioxolane (**20**) (10.2, 88%) $\{[\alpha]_D^{22} -17.4$ (c 1.4, $CHCl_3$), which showed an identical NMR spectrum to that above.

3.1.12. (2S,3R)-3-Methyl-henicosane-1,2-diol (21). *p*-Toluenesulfonic acid monohydrate (1 g, 5.26 mmol) was added

to a stirred solution of (*S*)-2,2-dimethyl-4-((*R*)-1-methylnonadecyl)-[1,3]dioxolane (**19**) (10.6 g, 27.7 mmol) in tetrahydrofuran (40 mL), methanol (50 mL) and water (5 mL) at room temperature and then refluxed for 2 h. The solvent was evaporated and the residue was diluted with petrol/ether (1:1, 150 mL) and then satd aq sodium bicarbonate (50 mL) was added. The aqueous layer was re-extracted with ether (2×70 mL). The combined organic layers were washed with satd aq sodium chloride (250 mL), dried and evaporated to give a white solid (2*S*,3*R*)-3-methyl-henicosane-1,2-diol (**21**) (8.95 g, 94%). A small amount of the compound was purified by chromatography on silica eluting with petrol/ethyl acetate (1:1) for analysis, mp 68–67 °C [found $[M-H]^+$: 341.3404; $C_{22}H_{45}O_2$ requires: 341.3414] $\{[\alpha]_D^{22} +12.7$ (*c* 1.11, $CHCl_3$)}, which showed δ_H (500 MHz, $CDCl_3$): 3.69–3.67 (1H, m), 3.62–3.54 (2H, m), 2.13 (1H, br s), 2.08 (1H, br s), 1.74–1.68 (1H, br m), 1.60–1.53 (2H, m), 1.46–1.23 (31H, m), 1.19–1.13 (1H, m), 0.94 (3H, d, *J* 6.6 Hz), 0.89 (3H, t, *J* 7.0 Hz); δ_C (125 MHz, $CDCl_3$): 75.8, 65.2, 35.7, 33.0, 31.9, 29.9, 29.70, 29.67, 29.4, 27.1, 22.7, 14.6, 14.1; ν_{max} : 3420 cm^{-1} .

3.1.13. (2*R*,3*S*)-3-Methyl-henicosane-1,2-diol (25). *p*-Toluenesulfonic acid monohydrate (1.6 g, 8.4 mmol) was added to a stirred solution of (*R*)-2,2-dimethyl-4-((*S*)-1-methylnonadecyl)-[1,3]dioxolane (**20**) (16.35 g, 42.7 mmol) in tetrahydrofuran (60 mL), methanol (90 mL) and water (5 mL) at room temperature, refluxed for 4.5 h, then worked up and purified as above to give (2*R*,3*S*)-3-methyl-henicosane-1,2-diol (**25**) as a white solid (14.7 g, 97%) $\{[\alpha]_D^{22} -12.9$ (*c* 1.34, $CHCl_3$)}, which showed an identical NMR spectrum to that above.

3.1.14. (S)-2-((R)-1-Methylnonadecyl)oxirane (22). Sodium hydroxide solution (50%, 34 mL) was added with vigorous stirring to (2*S*,3*R*)-3-methyl-henicosane-1,2-diol (**21**) (8.9 g, 26.1 mmol) and cetrimide (0.5 g) in dichloromethane (250 mL) at room temperature. A solution of *p*-toluenesulfonyl chloride (6.1 g, 32 mmol) in dichloromethane (32 mL) was then added over 10 min. The mixture was stirred for 30 min when TLC showed that no starting material was left and then quenched with water (150 mL). The aqueous layer was extracted with dichloromethane (2×50 mL). The combined organic layers were washed with water (100 mL), dried and evaporated to give a residue. Chromatography on silica eluting with petrol/ether (10:0.5) gave (*S*)-2-((*R*)-1-methylnonadecyl)oxirane (**22**) as a white solid (8.23 g, 97%), mp 45–47 °C [found $[M+H]^+$: 325.3470; $C_{22}H_{45}O$ requires: 325.3470] $\{[\alpha]_D^{22} +0.3$ (*c* 1.0, $CHCl_3$)}, which showed δ_H (500 MHz, $CDCl_3$): 2.78 (1H, dd, *J* 4.1, 5.2 Hz), 2.71–2.68 (1H, m), 2.54 (1H, dd, *J* 2.9, 5.2 Hz), 1.45–1.25 (34H, m), 1.18–1.13 (1H, m), 1.04 (3H, d, *J* 6.3 Hz), 0.90 (3H, t, *J* 6.7 Hz); δ_C (125 MHz, $CDCl_3$): 57.2, 47.0, 36.2, 33.6, 31.9, 29.9, 29.7, 29.68, 29.6, 29.4, 27.1, 22.7, 17.1, 14.1; ν_{max} : 2919, 1473, 1261, 892, 729 cm^{-1} .

3.1.15. (R)-2-((S)-1-Methylnonadecyl)oxirane. Sodium hydroxide solution (50%, 50 mL) was added to a vigorously stirred solution of (2*R*,3*S*)-3-methyl-henicosane-1,2-diol (14.7 g, 42.9 mmol) and cetrimide (0.82 g) in dichloromethane (450 mL) at room temperature. To this, a solution of *p*-toluene-sulfonyl chloride (10 g, 52.5 mmol) in dichloromethane (50 mL) was added over 10 min. The mixture was

stirred for 30 min, then worked up and purified as above to give (*R*)-2-((*S*)-1-methylnonadecyl)oxirane (12.8 g, 92%) $\{[\alpha]_D^{22} -0.66$ (*c* 1.054, $CHCl_3$)}, which showed an identical NMR spectrum to that above.

3.1.16. (8*R*,9*R*)-9-Methyl-1-(tetrahydropyran-2-yloxy)-heptacosan-8-ol (23). A solution of 1-bromo-6-tetrahydropyran-2-yloxyhexane (11.26 g, 42.4 mmol) in tetrahydrofuran (25 mL) was added dropwise to a suspension of magnesium turnings (2.1 g, 86 mmol) in tetrahydrofuran (30 mL) under nitrogen. The mixture was refluxed for 2 h, then cooled to room temperature and added dropwise to a stirred solution of purified copper iodide⁴¹ (0.75 g, 3.9 mmol) in dry tetrahydrofuran (30 mL) at –30 °C. After 10 min, a solution of (*S*)-2-((*R*)-1-methylnonadecyl)oxirane (**22**) (5.5 g, 16.94 mol) in tetrahydrofuran (10 mL) was added dropwise. The mixture was stirred for 3 h at –30 °C, allowed to reach –15 °C, then quenched with satd aq ammonium chloride (100 mL) and allowed to reach room temperature. The product was extracted with 1:1 petrol/ether (3×200 mL). The combined organic layers were washed with satd aq sodium chloride (250 mL), dried and evaporated to give a colourless oil. Chromatography on silica eluting with 5:2 petrol/ethyl acetate gave (8*R*,9*R*)-9-methyl-1-(tetrahydropyran-2-yloxy)-heptacosan-8-ol (**23**) as a colourless oil (6.35 g, 75%) [found $[M+Na]^+$: 533.4885; $C_{33}H_{66}O_3Na$ requires: 533.4904] $\{[\alpha]_D^{22} +9.15$ (*c* 1.3, $CHCl_3$)}, which showed δ_H (500 MHz, $CDCl_3$): 4.59 (1H, br s), 3.91–3.87 (1H, m), 3.74 (1H, td, *J* 7.0, 9.5 Hz), 3.54–3.51 (2H, m), 3.40 (1H, td, *J* 6.6, 9.5 Hz), 1.87–1.82 (1H, m), 1.75–1.69 (2H, m), 1.65–1.52 (6H, m), 1.48–1.25 (44H, m), 1.21–1.14 (1H, m), 0.90 (3H, t, *J* 7.0 Hz), 0.88 (3H, d, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 98.9, 75.2, 67.7, 62.3, 38.2, 34.4, 33.4, 31.9, 30.8, 30.0, 29.74, 29.70, 29.66, 29.6, 29.5, 29.4, 27.4, 26.24, 26.2, 25.5, 22.7, 19.7, 14.1, 13.6; ν_{max} : 3450, 2921, 2851, 1465, 1033 cm^{-1} .

3.1.17. (8*S*,9*S*)-9-Methyl-1-(tetrahydropyran-2-yloxy)-heptacosan-8-ol. 1-Bromo-6-tetrahydropyran-2-yloxyhexane (20.4 g, 76.9 mmol) in tetrahydrofuran (75 mL) was added dropwise to a suspension of magnesium turnings (3.85 g, 158.36 mmol) in tetrahydrofuran (50 mL) under nitrogen. The mixture was refluxed for 2 h, then cooled to room temperature and added dropwise to a stirred solution of purified copper iodide (1.36 g, 7.14 mmol) in dry tetrahydrofuran (70 mL) at –30 °C. After 30 min, a solution of (*R*)-2-((*S*)-1-methylnonadecyl)oxirane (10 g, 30.8 mmol) in tetrahydrofuran (60 mL) was added dropwise. The mixture was stirred for 3 h at –30 °C, allowed to reach –5 °C, then worked up and purified as above to give (8*S*,9*S*)-9-methyl-1-(tetrahydropyran-2-yloxy)-heptacosan-8-ol as a colourless oil (10.08 g, 64%) $\{[\alpha]_D^{22} -9.49$ (*c* 1.32, $CHCl_3$)}, which showed an identical NMR spectrum to that above.

3.1.18. 2-((8*R*,9*R*)-8-Methoxy-9-methylheptacosyloxy)-tetrahydropyran (24). Sodium hydride (3.4 g, 85 mmol, 60% dispersion) was washed with petrol (3×20 mL) and then suspended in dry tetrahydrofuran (35 mL), cooled to 5 °C and (8*R*,9*R*)-9-methyl-1-(tetrahydropyran-2-yloxy)-heptacosan-8-ol (**23**) (6.5 g, 12.76 mmol) in tetrahydrofuran (35 mL) was added over 5 min. After 15 min, methyl iodide (10.72 g, 75 mmol) was added. The mixture was stirred for 16 h at room temperature. Satd aq ammonium chloride

(50 mL) was added carefully followed by ether (100 mL). The aqueous layer was extracted with 1:1 petrol/ether (2×50 mL). The combined organic layers were washed with brine (2×80 mL), dried and evaporated to give a residue; chromatography on silica eluting with 10:2 petrol/ether gave 2-((8*R*,9*R*)-8-methoxy-9-methylheptacosyloxy)tetrahydropyran (**24**) (6.25 g, 94%) as a pale yellow oil [found $[M+Na]^+$: 547.5065; $C_{34}H_{68}O_3Na$ requires: 547.5061] $\{[\alpha]_D^{22} +8.76$ (c 1.45, $CHCl_3$)}, which showed δ_H (500 MHz, $CDCl_3$): 4.59 (1H, br t, J 2.3 Hz), 3.91–3.87 (1H, m), 3.74 (1H, td, J 7.0, 9.5 Hz), 3.53–3.49 (1H, m), 3.39 (1H, td, J 6.6, 9.5 Hz), 3.35 (3H, s), 2.99–2.95 (1H, m), 1.87–1.82 (1H, m), 1.76–1.71 (1H, m), 1.68–1.52 (6H, m), 1.45–1.25 (44H, m), 1.15–1.07 (1H, m), 0.89 (3H, t, J 7.0 Hz), 0.86 (3H, d, J 6.7 Hz); δ_C (125 MHz, $CDCl_3$): 98.8, 85.4, 67.7, 62.3, 57.7, 35.3, 32.4, 31.9, 30.8, 30.5, 30.0, 29.9, 29.8, 29.7, 29.67, 29.5, 29.4, 27.6, 26.2, 26.1, 25.5, 22.7, 19.7, 14.9, 14.1; ν_{max} : 2928, 2846, 1077 cm^{-1} .

3.1.19. 2-((8*S*,9*S*)-8-Methoxy-9-methylheptacosyloxy)-tetrahydropyran (26**).** Sodium hydride (5.5 g, 137.5 mmol, 60% dispersion) was washed with petrol (3×30 mL), suspended in dry tetrahydrofuran (60 mL), cooled to 5 °C and (8*S*,9*S*)-9-methyl-1-(tetrahydropyran-2-yloxy)heptacosan-8-ol (10.0 g, 19.57 mmol) in tetrahydrofuran (60 mL) was added over 5 min. After 15 min, methyl iodide (16.19 g, 114 mmol) was added, stirred for 16 h at room temperature, then worked up and purified as above to give 2-((8*S*,9*S*)-8-methoxy-9-methylheptacosyloxy)tetrahydropyran (**26**) (10.32 g, 100%) $\{[\alpha]_D^{22} -7.35$ (c 1.577, $CHCl_3$)}, which showed an identical NMR spectrum to that above.

3.1.20. (8*R*,9*R*)-8-Methoxy-9-methylheptacosan-1-ol (27**).** *p*-Toluenesulfonic acid monohydrate (0.543 g, 2.85 mmol) was added to a stirred solution of 2-((8*R*,9*R*)-8-methoxy-9-methylheptacosyloxy)tetrahydropyran (**24**) (6.0 g, 11.43 mmol) in tetrahydrofuran (20 mL), methanol (70 mL) and water (1 mL) at room temperature. The mixture was refluxed for 30 min, then evaporated to approximately half its volume and diluted with satd aq sodium bicarbonate (50 mL) and a mixture of 1:1 petrol/ether (150 mL) was added. The aqueous layer was re-extracted with petrol/ether (2×50 mL). The combined organic layers were washed with satd aq sodium chloride (100 mL), dried and evaporated to give a residue, which was purified by chromatography on silica eluting with 5:2 petrol/ether to give (8*R*,9*R*)-8-methoxy-9-methylheptacosan-1-ol (**27**) (4.1 g, 81%) as a colourless liquid, which solidified later, mp 33–35 °C, $\{[\alpha]_D^{22} +11.05$ (c 1.19, $CHCl_3$)}, which showed δ_H (500 MHz, $CDCl_3$): 3.65 (2H, t, J 6.6 Hz), 3.36 (3H, s), 2.98–2.95 (1H, m), 1.67–1.62 (1H, m), 1.58 (2H, pent, J 6.6 Hz), 1.49 (1H, br s), 1.45–1.25 (43H, m), 1.15–1.06 (1H, m), 0.89 (3H, t, J 6.7 Hz), 0.86 (3H, d, J 7.0 Hz); δ_C (125 MHz, $CDCl_3$): 85.5, 63.0, 57.7, 35.3, 32.8, 32.3, 31.9, 30.5, 30.0, 29.9, 29.7, 29.67, 29.4, 29.38, 27.6, 26.1, 25.7, 22.7, 14.9, 14.1; ν_{max} : 3463, 2912, 2846, 1078 cm^{-1} .

3.1.21. (8*S*,9*S*)-8-Methoxy-9-methylheptacosan-1-ol (28**).** *p*-Toluenesulfonic acid monohydrate (1.0 g, 5.25 mmol) was added to a stirred solution of 2-((8*S*,9*S*)-8-methoxy-9-methylheptacosyloxy)tetrahydropyran (**26**) (10.0 g, 19.05 mmol) in tetrahydrofuran (40 mL), methanol (70 mL) and water (1 mL) at room temperature. The mixture was

refluxed for 30 min, then worked up and purified as above to give (8*S*,9*S*)-8-methoxy-9-methylheptacosan-1-ol (**28**) (8.00 g, 95%) $\{[\alpha]_D^{22} -10.74$ (c 1.20, $CHCl_3$)}, which showed an identical NMR spectrum to that above.

3.1.22. (8*R*,9*R*)-8-Methoxy-9-methylheptacosanal (29**).** (8*R*,9*R*)-8-Methoxy-9-methylheptacosan-1-ol (**27**) (4.0 g, 9.1 mmol) in dichloromethane (30 mL) was added to a vigorously stirred suspension of pyridinium chlorochromate (4.9 g, 22.7 mmol) in dichloromethane (200 mL) at room temperature. The mixture was refluxed for 45 min, when TLC showed no starting material, then cooled and poured into ether (200 mL). It was filtered through a pad of silica, then washed with ether and the filtrate was evaporated. Chromatography on silica eluting with 10:1 petrol/ether gave (8*R*,9*R*)-8-methoxy-9-methylheptacosanal (**29**) (3.5 g, 87%) as a colourless liquid [found $[M+Na]^+$: 461.4312; $C_{29}H_{58}O_2Na$ requires: 461.4329], $\{[\alpha]_D^{22} +11.6$ (c 1.16, $CHCl_3$)}, which showed δ_H (500 MHz, $CDCl_3$): 9.77 (1H, t, J 1.9 Hz), 3.34 (3H, s), 2.97–2.93 (1H, m), 2.43 (2H, dt, J 1.9, 7.3 Hz), 1.64 (2H, br pent, J 7.3 Hz), 1.45–1.22 (42H, m), 1.11–1.05 (1H, m), 0.88 (3H, t, J 7.0 Hz), 0.85 (3H, d, J 7.0 Hz); δ_C (125 MHz, $CDCl_3$): 202.9, 85.5, 57.7, 43.9, 35.3, 32.3, 30.0, 29.7, 29.66, 29.6, 29.2, 27.6, 26.0, 22.7, 22.1, 14.9, 14.1; ν_{max} : 2924, 2850, 1729, 1465, 1097 cm^{-1} .

3.1.23. (8*S*,9*S*)-8-Methoxy-9-methylheptacosanal (30**).** (8*S*,9*S*)-8-Methoxy-9-methylheptacosan-1-ol (**28**) (7.9 g, 17.92 mmol) in dichloromethane (50 mL) was added to a stirred suspension of pyridinium chlorochromate (7.2 g, 33.4 mmol) in dichloromethane (250 mL) at room temperature. The mixture was stirred vigorously and refluxed for 45 min, then worked up and purified as above to give (8*S*,9*S*)-8-methoxy-9-methylheptacosanal (**30**) (6.5 g, 83%) $\{[\alpha]_D^{22} -11.3$ (c 1.50, $CHCl_3$)}, which showed an identical NMR spectrum to that above.

3.1.24. 2,2-Dimethylpropionic acid (16*R*,17*R*)-16-methoxy-17-methylpentatriacontyl ester (32**).** Lithium hexamethyldisilazide (14.35 mL, 14.35 mmol, 1.0 M) was added dropwise to a stirred solution of (8*R*,9*R*)-8-methoxy-9-methylheptacosanal (**29**) (3.4 g, 7.74 mmol) and 5-(1-octanolpivalate-8-sulfonyl)-1-phenyl-1*H*-tetrazole (**31**) (see Supplementary data) (4.04 g, 9.57 mmol) in dry tetrahydrofuran (100 mL) under nitrogen at –2 °C. The mixture was allowed to reach room temperature and stirred for 16 h, then quenched with satd 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, 2×50 mL). The combined organic layers were washed with satd aq sodium chloride (2×100 mL), dried and evaporated to give a thick oil, which was purified by chromatography on silica eluting with petrol/ether (10:0.3) to give (*E/Z*)-2,2-dimethylpropionic acid (16*R*,17*R*)-16-methoxy-17-methylpentatriacont-8-enyl ester (2.6:1, *E/Z*) (4.45 g, 91%). Palladium on charcoal (10%, 1 g) was added to a solution of the esters (4.3 g, 6.77 mmol) in ethanol (150 mL). The mixture was stirred while being hydrogenated at atmospheric pressure. When no more hydrogen was absorbed it was filtered through a pad of Celite and washed with ethanol (100 mL). The filtrate was evaporated at 14 mm Hg to give 2,2-dimethylpropionic acid

(16*R*,17*R*)-16-methoxy-17-methylpentatriacontyl ester (**32**) (4.02 g, 93%) as a colourless liquid [found $[M+Na]^+$: 659.6293; $C_{42}H_{84}O_3Na$ requires: 659.6313] $\{[\alpha]_D^{22} +6.8$ (*c* 1.49, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.7 Hz), 3.34 (3H, s), 2.97–2.94 (1H, m), 1.62 (2H, pent, *J* 6.7 Hz), 1.46–1.22 (60H, m), 1.20 (9H, s), 1.12–1.06 (1H, m), 0.88 (3H, t, *J* 6.7 Hz), 0.85 (3H, d, *J* 7.0 Hz); δ_C (125 MHz, $CDCl_3$): 178.5, 85.4, 64.4, 57.7, 38.7, 35.3, 32.4, 31.9, 30.8, 30.5, 30.0, 29.9, 29.7, 29.69, 29.66, 29.6, 29.5, 29.4, 29.2, 28.6, 27.6, 27.2, 26.2, 25.9, 22.7, 14.8, 14.1; ν_{max} : 2923, 1731, 1154 cm^{-1} .

3.1.25. 2,2-Dimethylpropionic acid (16*S*,17*S*)-16-methoxy-17-methylpentatriacontyl ester (33). Lithium hexamethyldisilazide (24 mL, 25.44 mmol, 1.06 M) was added dropwise to a stirred solution of (8*S*,9*S*)-8-methoxy-9-methylheptacosanal (**30**) (6.4 g, 14.58 mmol) and 5-(1-octanolpivalate-8-sulfonyl)-1-phenyl-1*H*-tetrazole (**31**) (7.9 g, 18.7 mmol) in dry tetrahydrofuran (160 mL) under nitrogen at $-15^\circ C$. The mixture was allowed to reach room temperature, stirred for 16 h, then worked up as above to give (*E/Z*)-2,2-dimethylpropionic acid (16*S*,17*S*)-16-methoxy-17-methylpentatriacont-8-enyl ester as a colourless liquid (2.6:1, *E/Z*) (8.04 g, 87%). Hydrogenation and purification as above gave 2,2-dimethylpropionic acid (16*S*,17*S*)-16-methoxy-17-methylpentatriacontyl ester (**33**) as a colourless liquid (8.06, 100%) $\{[\alpha]_D^{22} -6.5$ (*c* 1.503, $CHCl_3$) $\}$, which showed an identical NMR spectrum to that above.

3.1.26. (16*R*,17*R*)-16-Methoxy-17-methylpentatriacontan-1-ol (34). Potassium hydroxide (1.5 g, 26.36 mmol) in methanol (20 mL) was added to a stirred solution of 2,2-dimethylpropionic acid (16*R*,17*R*)-16-methoxy-17-methylpentatriacontyl ester (**32**) (4.0 g, 6.28 mmol) in tetrahydrofuran (50 mL) at room temperature. The mixture was stirred at $40^\circ C$ for 3 h, then quenched with water (100 mL) and a mixture of petrol/ether (1:1, 100 mL). The aqueous layer was re-extracted with petrol/ether (2×50 mL). The combined organic layers were washed with brine (60 mL), dried and evaporated to give a white solid, (16*R*,17*R*)-16-methoxy-17-methylpentatriacontan-1-ol (**34**) (3.4 g, 98%), mp $46-48^\circ C$ [found $[M+H]^+$: 575.5749; $C_{37}H_{76}O_2Na$ requires: 575.5737] $\{[\alpha]_D^{22} +7.9$ (*c* 1.40, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 3.66 (2H, t, *J* 6.6 Hz), 3.36 (3H, s), 2.99–2.96 (1H, m), 1.67–1.64 (1H, m), 1.59 (2H, pent, *J* 6.6 Hz), 1.49 (1H, br s), 1.48–1.22 (59H, m), 1.14–1.07 (1H, m), 0.90 (3H, t, *J* 7.0 Hz), 0.87 (3H, d, *J* 6.7 Hz); δ_C (125 MHz, $CDCl_3$): 85.5, 63.1, 57.7, 35.3, 32.8, 32.4, 31.9, 30.5, 30.0, 29.9, 29.7, 29.68, 29.63, 29.5, 29.4, 27.6, 26.2, 25.7, 22.7, 14.9, 14.1; ν_{max} : 3373, 2921, 1098, 1076 cm^{-1} .

3.1.27. (16*S*,17*S*)-16-Methoxy-17-methylpentatriacontan-1-ol (35). Potassium hydroxide (3.4 g, 60.6 mmol) in methanol (35 mL) was added to a stirred solution of 2,2-dimethylpropionic acid (16*S*,17*S*)-16-methoxy-17-methylpentatriacontyl ester (**33**) (8.06 g, 12.65 mmol) in tetrahydrofuran (75 mL) at room temperature. The mixture was stirred at $40^\circ C$ for 3 h, followed by work up and purification as above to give (16*S*,17*S*)-16-methoxy-17-methylpentatriacontan-1-ol (**35**) as a white solid (6.63 g, 95%)

$\{[\alpha]_D^{22} -8.21$ (*c* 1.21, $CHCl_3$) $\}$, which showed an identical NMR spectrum to that above.

3.1.28. (16*R*,17*R*)-1-Bromo-16-methoxy-17-methylpentatriacontane. *N*-Bromosuccinimide (1.6 g, 9.00 mmol) was added in portions over 15 min to a stirred solution of (16*R*,17*R*)-16-methoxy-17-methylpentatriacontan-1-ol (**34**) (3.91 g, 7.07 mmol) and triphenylphosphine (2.1 g, 8 mmol) in dichloromethane (50 mL) at $0^\circ C$. The mixture was stirred at room temperature for 1 h and then quenched with satd aq sodium metabisulfite (50 mL). The aqueous layer was re-extracted with dichloromethane (2×30 mL). The combined organic layers were washed with water, dried and evaporated. The residue was treated with petrol/ether (1:1, 100 mL), refluxed for 30 min, then filtered and washed with petrol/ether (50 mL). The filtrate was evaporated and the residue was purified by chromatography on silica eluting with petrol/ether (10:0.2) to give (16*R*,17*R*)-1-bromo-16-methoxy-17-methylpentatriacontane (3.72 g, 85%) as a white solid, mp $38-40^\circ C$ [found: C, 72.4; H, 12.2; $C_{37}H_{75}OBr$ requires: C, 72.16; H, 12.27] $\{[\alpha]_D^{22} +6.5$ (*c* 1.158, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 3.43 (2H, t, *J* 7.0 Hz), 3.36 (3H, s), 2.99–2.96 (1H, m), 1.87 (2H, br pent, *J* 6.7 Hz), 1.68–1.62 (1H, m), 1.48–1.22 (59H, m), 1.15–1.08 (1H, m), 0.91 (3H, t, *J* 6.3 Hz), 0.87 (3H, d, *J* 6.9 Hz); δ_C (125 MHz, $CDCl_3$): 85.5, 57.7, 35.3, 34.0, 32.8, 32.4, 31.9, 30.5, 30.0, 29.9, 29.7, 29.6, 29.5, 29.45, 29.4, 28.8, 28.2, 27.6, 26.1, 22.7, 14.9, 14.1; ν_{max} : 2929, 2849, 1099, 717 cm^{-1} .

3.1.29. (16*S*,17*S*)-1-Bromo-16-methoxy-17-methylpentatriacontane. *N*-Bromosuccinimide (2.65 g, 14.9 mmol) was added in portions over 15 min to a stirred solution of (16*S*,17*S*)-16-methoxy-17-methylpentatriacontan-1-ol (**35**) (6.25 g, 11.3 mmol) and triphenylphosphine (3.35 g, 12.77 mmol) in dichloromethane (90 mL) at $0^\circ C$. After 1 h, work up and purification as above gave a white solid, (16*S*,17*S*)-1-bromo-16-methoxy-17-methylpentatriacontane (5.3 g, 76%) $\{[\alpha]_D^{22} -7.35$ (*c* 1.16, $CHCl_3$) $\}$, which showed an identical NMR spectra to that above.

3.1.30. 5-((16*R*,17*R*)-16-Methoxy-17-methylpentatriacontyl-1-sulfanyl)-1-phenyl-1*H*-tetrazole. (16*R*,17*R*)-1-Bromo-16-methoxy-17-methylpentatriacontane (3.05 g, 4.95 mmol) was added to a stirred solution of 1-phenyl-1*H*-tetrazol-5-thiol (0.98 g, 5.5 mmol) and potassium carbonate (2.7 g, 19.5 mmol) in acetone (60 mL) at room temperature. The mixture was stirred for 18 h, then the solvent was evaporated and the residue diluted with petrol/ether (1:1, 150 mL) and water (100 mL). The aqueous layer was extracted with the same solvent mixture (2×50 mL). The combined organic layers were dried and evaporated to give a pale yellow viscous oil; chromatography on silica eluting with 10:1 petrol/ether gave 5-((16*R*,17*R*)-16-methoxy-17-methylpentatriacontyl-1-sulfanyl)-1-phenyl-1*H*-tetrazole (3.21 g, 91%) as a colourless viscous oil [found $[M+Na]^+$: 735.5912; $C_{44}H_{80}ON_4SNa$ requires: 735.5945] $\{[\alpha]_D^{22} +6.18$ (*c* 1.21, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 7.59–7.51 (5H, m), 3.39 (2H, t, *J* 7.5 Hz), 3.34 (3H, s), 2.97–2.94 (1H, m), 1.82 (2H, br pent, *J* 7.5 Hz), 1.66–1.60 (1H, m), 1.48–1.22 (59H, m), 1.12–1.05 (1H, m), 0.88 (3H, t, *J* 6.6 Hz), 0.84 (3H, d, *J* 6.0 Hz); δ_C (125 MHz, $CDCl_3$): 154.0, 133.2, 129.7, 129.2, 123.3, 84.9, 57.2,

34.8, 32.8, 31.8, 31.4, 29.9, 29.45, 29.4, 29.1, 29.0, 28.9, 28.8, 28.55, 28.5, 28.1, 27.0, 25.6, 22.2, 14.4, 13.6; ν_{\max} : 2928, 2861, 1097 cm^{-1} .

3.1.31. 5-((16S,17S)-16-Methoxy-17-methylpentatriacontyl-1-sulfanyl)-1-phenyl-1H-tetrazole. (16S,17S)-1-Bromo-16-methoxy-17-methylpentatriacontane (9.91 g, 16.09 mmol) was added to a stirred solution of 1-phenyl-1H-tetrazol-5-thiol (3.2 g, 17.96 mmol) and potassium carbonate (5.6 g, 40.5 mmol) in acetone (200 mL) at room temperature. The mixture was stirred for 2 h at 40 °C, then at room temperature for 16 h, then worked up and purified as above to give 5-((16S,17S)-16-methoxy-17-methylpentatriacontyl-1-sulfanyl)-1-phenyl-1H-tetrazole as a colourless oil (11.34, 99%) $\{[\alpha]_{\text{D}}^{22} -6.5$ (*c* 1.32, CHCl_3), which showed an identical NMR spectrum to that above.

3.1.32. 5-((16R,17R)-16-Methoxy-17-methylpentatriacontane-1-sulfonyl)-1-phenyl-1H-tetrazole (36). To a stirred solution of 5-((16R,17R)-16-methoxy-17-methylpentatriacontylsulfanyl)-1-phenyl-1H-tetrazole (2.23 g, 3.13 mmol) in methylated spirit (70 mL) and tetrahydrofuran (30 mL) was added dropwise ammonium heptamolybdate(VI) tetrahydrate (3.8 g, 3.1 mmol) in ice cold hydrogen peroxide (35% w/w, 11 mL) at 5 °C. The resulting yellow solution was stirred for 1 h at room temperature and then another ice cold solution of ammonium heptamolybdate(VI) tetrahydrate (1.9 g) in hydrogen peroxide (5.5 mL) was added. The mixture was stirred at room temperature for 16 h and then dichloromethane (60 mL) was added followed by water (300 mL). The aqueous layer was re-extracted with dichloromethane (2×30 mL). The combined organic layers were washed with water, dried and evaporated to give a residue; chromatography on silica eluting with petrol/ether (10:1) gave 5-((16R,17R)-16-methoxy-17-methylpentatriacontane-1-sulfonyl)-1-phenyl-1H-tetrazole (36) as a white solid (1.91 g, 82%), mp 42–44 °C [found $[\text{M}+\text{Na}]^+$: 767.5869; $\text{C}_{44}\text{H}_{80}\text{O}_3\text{N}_4\text{SNa}$ requires: 767.5843] $\{[\alpha]_{\text{D}}^{22} +5.65$ (*c* 1.90, CHCl_3), which showed δ_{H} (500 MHz, CDCl_3): 7.73–7.71 (2H, m), 7.65–7.61 (3H, m), 3.75 (2H, distorted t, *J* 7.9 Hz), 3.36 (3H, s), 2.98–2.96 (1H, m), 1.97 (2H, br pent, *J* 7.5 Hz), 1.68–1.61 (2H, m), 1.52 (2H, br pent, *J* 7.5 Hz), 1.45–1.22 (56H, m), 1.15–1.07 (1H, m), 0.90 (3H, t, *J* 6.6 Hz), 0.87 (3H, d, *J* 6.9 Hz); δ_{C} (125 MHz, CDCl_3): 153.5, 133.1, 131.5, 129.7, 125.1, 85.5, 57.7, 56.0, 35.3, 32.4, 31.9, 30.5, 30.0, 29.97, 29.7, 29.65, 29.6, 29.5, 29.4, 29.2, 28.9, 28.2, 27.6, 26.2, 22.7, 21.9, 14.9, 14.1; ν_{\max} : 2924, 2849, 1343, 1157, 1096 cm^{-1} .

3.1.33. 5-((16S,17S)-16-Methoxy-17-methylpentatriacontane-1-sulfonyl)-1-phenyl-1H-tetrazole (37). To a stirred solution of 5-((16S,17S)-16-methoxy-17-methylpentatriacontylsulfanyl)-1-phenyl-1H-tetrazole (11.2 g, 15.7 mmol) in methylated spirit (250 mL) and tetrahydrofuran (200 mL) was added dropwise ammonium heptamolybdate(VI) tetrahydrate (18 g, 14.5 mmol) in ice cold hydrogen peroxide (35% w/w, 60 mL) at 5 °C. The resulting yellow solution was stirred for 1 h at room temperature and then another ice cold solution of ammonium heptamolybdate(VI) tetrahydrate (8 g) in hydrogen peroxide (30 mL) was added. After 16 h, work up and purification as above gave 5-((16S,17S)-16-methoxy-17-methylpentatriacontane-1-sulfonyl)-1-phenyl-1H-tetrazole (37) as a white solid, mp

44–46 °C (10.6 g, 91%) $\{[\alpha]_{\text{D}}^{22} -6.19$ (*c* 1.39, CHCl_3), which showed an identical NMR spectrum to that above.

3.1.34. 6-(1-Phenyl-1H-tetrazole-5-ylsulfanyl)hexane-1-ol (38). Anhydrous potassium carbonate (36 g, 260 mmol) was added to a stirred solution of 6-bromohexane-1-ol (20 g, 110.4 mmol) and 1-phenyl-1H-tetrazole-5-thiol in acetone (200 mL) at room temperature. The mixture was stirred at 40 °C for 2 h, at room temperature for 16 h and then diluted with water (1000 mL) and dichloromethane (200 mL). The aqueous layer was re-extracted with dichloromethane (2×150 mL). The combined organic layers were washed with water, brine and evaporated to give 6-(1-phenyl-1H-tetrazole-5-ylsulfanyl)hexane-1-ol (38) as a pale yellow oil (30.6 g, 99.5%) [found $[\text{M}+\text{H}]^+$: 279.1276; $\text{C}_{13}\text{H}_{19}\text{N}_4\text{OS}$ requires: 279.1274], which showed δ_{H} (500 MHz, CDCl_3): 7.53–7.48 (5H, br s), 3.59 (2H, t, *J* 6.3 Hz), 3.35 (2H, t, *J* 6.9 Hz), 2.47 (1H, br s), 1.78 (2H, pent, *J* 7.3 Hz), 1.53 (2H, pent, *J* 7.0 Hz), 1.47–1.35 (4H, m); δ_{C} (125 MHz, CDCl_3): 154.3, 133.4, 129.9, 129.6, 123.6, 62.2, 33.0, 32.2, 28.8, 28.1, 25.0; ν_{\max} : 3394, 2930 cm^{-1} .

3.1.35. 6-(1-Phenyl-1H-tetrazole-5-ylsulfonyl)hexane-1-ol (39). A solution of ammonium heptamolybdate(VI) tetrahydrate (22 g, 17.8 mmol) in ice cold H_2O_2 (35% w/w, 60 mL) was added dropwise at 5 °C to a stirred solution of 6-(1-phenyl-1H-tetrazole-5-ylsulfanyl)hexane-1-ol (38) (31 g, 111.3 mmol) in methylated spirit (300 mL) and tetrahydrofuran (250 mL). The resulting yellow solution was stirred for 1 h and then three more identical solutions of ammonium heptamolybdate(VI) tetrahydrate in H_2O_2 (35% w/w) were added over 1 h. The mixture was stirred at room temperature for 16 h and then diluted with water (1500 mL) and dichloromethane (300 mL). The aqueous layer was re-extracted with dichloromethane (2×200 mL). The combined organic layers were washed with water, brine, dried and evaporated to give the product. Chromatography on silica eluting with 1:1 petrol/ethyl acetate gave 6-(1-phenyl-1H-tetrazole-5-ylsulfonyl)hexane-1-ol (39) as a colourless oil, which solidified later (31.03 g, 90%) [found $[\text{M}+\text{Na}]^+$: 333.0954; $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_3\text{S}$ requires: 333.0992], which showed δ_{H} (500 MHz, CDCl_3): 7.67–7.66 (2H, m), 7.63–7.54 (3H, m), 3.72 (2H, distorted t, *J* 7.8 Hz), 3.61 (2H, t, *J* 6.3 Hz), 1.95 (2H, pent, *J* 7.5 Hz), 1.83 (1H, br s), 1.58–1.49 (4H, m), 1.45–1.38 (2H, m); δ_{C} (125 MHz, CDCl_3): 153.4, 132.9, 131.4, 129.6, 125.0, 62.3, 55.7, 32.0, 27.7, 25.0, 21.8; ν_{\max} : 3315, 3073, 2909, 1592, 1496, 1472, 1349 cm^{-1} .

3.1.36. 5-(6-Bromohexane-1-sulfonyl)-1-phenyl-1H-tetrazole (40). *N*-Bromosuccinimide (6.8 g, 38.25 mmol) was added in portions over 20 min to a stirred solution of 6-(1-phenyl-1H-tetrazole-5-ylsulfonyl)hexane-1-ol (39) (9.3 g, 30 mmol) and triphenylphosphine (9.8 g, 37.4 mmol) in dichloromethane (160 mL) at 0 °C. The mixture was stirred at room temperature for 16 h and then quenched with satd aq sodium metabisulfite (50 mL). The aqueous layer was re-extracted with dichloromethane (2×100 mL). The combined organic layers were washed with water, dried and evaporated to give a residue. This was treated with ether (200 mL), refluxed for 30 min and the triphenylphosphonium oxide filtered off and washed with ether. The filtrate

was evaporated and the residue purified by chromatography on silica eluting with 5:2 petrol/ethyl acetate to give 5-(6-bromohexane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**40**) (9.6 g, 86%) as a white solid [found $[M+Na]^+$: 395.0121; $C_{13}H_{17}N_4O_2S^{79}Br$ requires: 395.0148], which showed δ_H (500 MHz, $CDCl_3$): 7.68–7.67 (2H, m), 7.63–7.57 (3H, m), 3.73 (2H, distorted t, J 7.9 Hz), 3.39 (2H, t, J 7.0 Hz), 1.97 (2H, pent, J 6.6 Hz), 1.86 (2H, pent, J 7.0 Hz), 1.58–1.48 (4H, m); δ_C (125 MHz, $CDCl_3$): 153.4, 133.0, 131.4, 129.6, 125.0, 55.8, 33.3, 32.1, 27.3, 27.2, 21.8, 15.2; ν_{max} : 2929, 2849, 1099, 717 cm^{-1} .

3.1.37. Butyric acid (1*S*,2*R*)-2-(7-bromoheptyl)cyclopropyl methyl ester (42). Lithium hexamethyldisilazide (30 mL, 31.8 mmol, 1.06 M) was added dropwise to a stirred solution of (1*S*,2*R*)-1-butylloxymethyl-2-formylcyclopropane (**41**) (5.3 g, 31.1 mmol) and 5-(6-bromohexane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**40**) (12.4 g, 33.2 mmol) in dry tetrahydrofuran (150 mL) under nitrogen at $-20^\circ C$. The mixture was allowed to reach room temperature, stirred for 16 h, then quenched with satd aq ammonium chloride (200 mL) and petrol/ether (1:1, 200 mL). The aqueous layer was re-extracted with petrol/ether (1:1, 2×200 mL). The combined organic layers were washed with a satd aq sodium chloride (2×100 mL), dried and evaporated to give a thick oil. Chromatography on silica eluting with 10:1 petrol/ether gave butyric acid (1*S*,2*R*)-2-((*E/Z*)-7-bromohept-1-enyl)cyclopropyl methyl ester (1:0.27) (7.71 g, 78%). 2,4,6-Triisopropylbenzene sulfonylhydrazide (14.1 g, 47.28 mmol) was added to a stirred solution of the esters (7.5 g, 23.6 mmol) in tetrahydrofuran (70 mL) at room temperature. The mixture was stirred at $52^\circ C$ for 3 h, followed by the addition of another mole equivalent of the hydrazide and stirring under the same conditions for 24 h. It was diluted with petrol/ether (1:1, 100 mL) and washed with aq sodium hydroxide (2%, 200 mL). The aqueous layer was re-extracted with ether (2×100 mL). The combined organic layers were washed with water and dried to give an oil. 1H NMR showed that less than 5% starting material was left; the residue was dissolved in dichloromethane (75 mL) and acetic acid (7 mL), then cetrimide (0.4 g) and water (75 mL) were added. The two phase mixture was stirred vigorously and potassium permanganate (2.4 g, 15 mmol) was added. After 1.5 h, sodium metabisulfite was added to destroy the excess of potassium permanganate and to dissolve MnO_2 . The mixture was diluted with petrol/ether (1:1, 100 mL). The aqueous layer was re-extracted with ether (2×100 mL). The combined organic layers were washed with water, dried and evaporated; chromatography on silica eluting with 10:1 petrol/ether gave butyric acid (1*S*,2*R*)-2-(7-bromoheptyl)cyclopropyl methyl ester (**42**) (5.2 g, 67%) as a pale yellow oil $\{[\alpha]_D^{25} -14.31$ (c 1.20, $CHCl_3$)} [found $[M+Na]^+$: 341.1083; $C_{15}H_{27}O_2^{79}BrNa$ requires: 341.1087], which showed δ_H (500 MHz, $CDCl_3$): 4.18 (1H, dd, J 6.9, 11.7 Hz), 3.92 (1H, dd, J 8.8, 11.7 Hz), 3.39 (2H, t, J 6.9 Hz), 2.28 (2H, t, J 7.3 Hz), 1.84 (2H, pent, J 7.0 Hz), 1.64 (2H, sext, J 7.3 Hz), 1.45–1.35 (5H, m), 1.34–1.27 (4H, m), 1.25–1.17 (1H, m), 1.14–1.07 (1H, m), 0.94 (3H, t, J 7.6 Hz), 0.88–0.82 (1H, m), 0.73 (1H, dt, J 4.7, 8.5 Hz), 0.01 (1H, br q, J 5.4 Hz); δ_C (125 MHz, $CDCl_3$): 173.7, 65.0(+), 36.3(+), 33.8(+), 32.7(+), 29.8(+), 29.2(+), 28.7(+), 28.5(+), 28.1(+), 18.5(+),

16.1(–), 14.2(–), 13.6(–), 9.7(+); ν_{max} : 2922, 1732, 1464, 798 cm^{-1} .

3.1.38. [(1*S*,2*R*)-2-(7-Bromoheptyl)cyclopropyl]methanol (43). Anhydrous potassium carbonate (6 g, 43.4 mmol) was added to a stirred solution of butyric acid (1*S*,2*R*)-2-(7-bromoheptyl)cyclopropyl methyl ester (**42**) (5.2 g, 16.35 mmol) in methanol (30 mL) and THF (20 mL) at room temperature. After 4 h at $45^\circ C$, it was diluted with water (200 mL) and ether (100 mL). The aqueous layer was re-extracted with ether (2×50 mL). The combined organic layers were washed with brine, dried and evaporated; chromatography on silica eluting with 10:2 petrol/ether gave [(1*S*,2*R*)-2-(7-bromoheptyl)cyclopropyl]methanol as a colourless oil (**43**) (3.42 g, 84%) $\{[\alpha]_D^{25} -18.9$ (c 1.04, $CHCl_3$)} [found $[M+H]^+$: 249.0841; $C_{11}H_{22}OBr$ requires: 249.0849], which showed δ_H (500 MHz, $CDCl_3$): 3.62 (1H, dd, J 7.3, 11.4 Hz), 3.55 (1H, dd, J 8.2, 11.4 Hz), 3.38 (2H, t, J 7.0 Hz), 1.83 (2H, br pent, J 7.0 Hz), 1.56 (1H, br s), 1.46–1.36 (5H, m), 1.35–1.27 (4H, m), 1.24–1.17 (1H, m), 1.11–1.03 (1H, m), 0.87–0.80 (1H, m), 0.68 (1H, dt, J 4.8, 8.6 Hz), -0.06 (1H, br q, J 5.4 Hz); δ_C (125 MHz, $CDCl_3$): 63.1(+), 33.9(+), 32.7(+), 29.9(+), 29.2(+), 28.6(+), 28.4(+), 28.1(+), 18.0(–), 16.0(–), 9.4(+); ν_{max} : 3376, 2921, 1029, 722 cm^{-1} .

3.1.39. (1*S*,2*R*)-2-(7-Bromoheptyl)cyclopropane carbaldehyde (44). [(1*S*,2*R*)-2-(7-Bromoheptyl)cyclopropyl]methanol (**43**) (1.5 g, 6.0 mmol) in dichloromethane (10 mL) was added to a stirred suspension of pyridinium chlorochromate (2.2 g, 10.2 mmol) in dichloromethane (35 mL) at room temperature. The mixture was stirred vigorously for 3 h, then poured into ether (200 mL) and filtered through a pad of silica, then washed with ether and the filtrate was evaporated. Chromatography on silica eluting with petrol/ether (5:0.5) gave (1*S*,2*R*)-2-(7-bromoheptyl)cyclopropanecarbaldehyde (**44**) as a colourless oil (1.38 g, 93%) $\{[\alpha]_D^{25} -10.1$ (c 1.62, $CHCl_3$)} [found $[M+Na]^+$: 269.0486; $C_{11}H_{19}O^{79}BrNa$ requires: 269.0511], which showed δ_H (500 MHz, $CDCl_3$): 9.34 (1H, d, J 5.4 Hz), 3.38 (2H, t, J 6.9 Hz), 1.88–1.79 (3H, m), 1.61–1.54 (1H, m), 1.51–1.43 (2H, m), 1.42–1.35 (3H, m), 1.32–1.25 (5H, m), 1.21 (1H, dt, J 4.8, 7.9 Hz), 1.15 (1H, td, J 5.1, 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 201.7(–), 33.9(+), 32.7(+), 29.7(+), 28.9(+), 28.5(+), 28.0(+), 27.96(+), 27.7(–), 24.7(–), 14.7(+); ν_{max} : 2930, 2852, 1698, 1463, 1177, 1055, 643 cm^{-1} .

3.1.40. (1*R*,2*S*)-1-(7-Bromoheptyl)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (45). Lithium hexamethyldisilazide (6 mL, 6.36 mmol, 1.06 M) was added dropwise to a stirred solution of (1*S*,2*R*)-2-(7-bromoheptyl)cyclopropanecarbaldehyde (**44**) (1.3 g, 5.26 mmol) and 5-((16*R*,17*R*)-16-methoxy-17-methylpentatriacontane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**36**) (3.72 g, 5.0 mmol) in dry tetrahydrofuran (60 mL) under nitrogen at $-15^\circ C$. The mixture was allowed to reach room temperature and stirred for 16 h, then quenched with a satd aq ammonium chloride (100 mL) and diluted with petrol/ether (1:1, 100 mL). The aqueous layer was re-extracted with petrol/ether (1:1, 2×75 mL). The combined organic layers were washed with brine, dried and evaporated to give a pale yellow oil; chromatography on silica eluting with petrol/ether (10:1)

gave (1*R*,2*S*)-1-(7-bromoheptyl)-2-(*Z/E*)-(17*R*,18*R*)-17-methoxy-18-methylhexatriacont-1-enyl)cyclopropane (6:1 *Z/E*) (3.38 g, 92%) as a colourless liquid, which solidified later. 2,4,6-Triisopropylbenzene sulfonylhydrazide (2.7 g, 9.0 mmol) was added to a stirred solution of the above cyclopropanes (3.3 g, 4.31 mmol) in tetrahydrofuran (25 mL) at room temperature and stirred at 52 °C for 3 h, followed by the addition of another mole equivalent of the hydrazide and stirring under the same condition for 24 h. The mixture was diluted with petrol/ether (1:1, 100 mL) and washed with aq sodium hydroxide (100 mL, 2%). The aqueous layer was re-extracted with petrol/ether (1:1, 2×50 mL). The combined organic layers were washed with brine, dried and evaporated to give a colourless residue (3.63 g). ¹H NMR showed that a very small amount of starting material was left. The residue was dissolved in dichloromethane (25 mL) and to this were added acetic acid (2 mL), cetrimide (0.2 g) and water (50 mL). The two phase mixture was vigorously stirred and potassium permanganate (0.5 g) was added. After 1.5 h, it was worked up as before to give a residue; chromatography on silica eluting with petrol/ether (10:0.5) gave a white solid, (1*R*,2*S*)-1-(7-bromoheptyl)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (**45**) (3.03 g, 91%), mp 32–34 °C {[α]_D²²+5.5 (c 1.29, CHCl₃)}, which showed δ_H (500 MHz, CDCl₃): 3.41 (2H, t, *J* 6.9 Hz), 3.35 (3H, s), 2.98–2.95 (1H, m), 1.87 (2H, pent, *J* 6.7 Hz), 1.68–1.62 (1H, m), 1.48–1.22 (72H, br m), 1.18–1.08 (4H, m), 0.9 (3H, t, *J* 7.0 Hz), 0.87 (3H, d, *J* 7.0 Hz), 0.72–0.62 (2H, m), 0.58 (1H, dt, *J* 4.1, 8.0 Hz), –0.31 (1H, br q, *J* 5.1 Hz); δ_C (125 MHz, CDCl₃): 85.4(–), 57.7(–), 35.4(–), 33.9, 32.9(+), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.1(+), 30.0(+), 29.9(+), 29.7(+), 29.42(+), 29.4(+), 28.8(+), 28.7(+), 28.65(+), 28.2(+), 27.6(+), 26.2(+), 22.7(+), 15.8(–), 15.7(–), 14.9(–), 14.1(–), 10.9(+); ν_{max}: 2922, 1464, 1098, 720 cm^{–1}.

3.1.41. (1*R*,2*S*)-1-(7-Bromoheptyl)-2-((17*S*,18*S*)-17-methoxy-18-methylhexatriacontyl)cyclopropane. Lithium hexamethyldisilazide (15.0 mL, 15.9 mmol, 1.06 M) was added dropwise to a stirred solution of (1*S*,2*R*)-2-(7-bromoheptyl)cyclopropanecarbaldehyde (**44**) (3.1 g, 12.54 mmol) and 5-((16*S*,17*S*)-16-methoxy-17-methylpentatriacontane-1-sulfonyl)-1-phenyl-1*H*-tetrazole (**37**) (9.4 g, 12.6 mmol) in dry tetrahydrofuran (150 mL) under nitrogen at –15 °C. The mixture was allowed to reach room temperature and stirred for 16 h, then worked up and purified as above to give (1*R*,2*S*)-1-(7-bromoheptyl)-2-(*Z/E*)-(17*S*,18*S*)-17-methoxy-18-methylhexatriacont-1-enyl)cyclopropane (6:1) (8.35 g, 87%) as a colourless liquid, which solidified later. Hydrogenation and purification as above gave (1*R*,2*S*)-1-(7-bromoheptyl)-2-((17*S*,18*S*)-17-methoxy-18-methylhexatriacontyl)cyclopropane as a thick yellow liquid (7.22 g, 75%) {[α]_D²²–5.84 (c 1.16, CHCl₃)}, which showed an identical NMR spectrum to that above.

3.1.42. 5-{7-[(1*R*,2*S*)-2-((17*R*,18*R*)-17-Methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (46**).** (1*R*,2*S*)-1-(7-Bromoheptyl)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (**45**) (2.9 g, 3.78 mmol) in tetrahydrofuran (10 mL) was added to a stirred solution of 1-phenyl-1*H*-tetrazol-5-thiol (0.75 g, 4.2 mmol) and potassium carbonate (2 g, 14.5 mmol) in acetone (50 mL) at room temperature. The

mixture was stirred for 5 h at 40 °C, at room temperature for 16 h and then diluted with water (50 mL) and dichloromethane (100 mL). The aqueous layer was re-extracted with dichloromethane (2×50 mL). The combined organic layers were washed with water, brine, dried and evaporated. Chromatography on silica eluting with 10:1 petrol/ether gave 5-{7-[(1*R*,2*S*)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (**46**) (3.21 g, 91%) as a colourless viscous oil {[α]_D²²+3.9 (c 1.21, CHCl₃)} [found [M+Na]⁺: 887.7553; C₅₅H₁₀₀N₄OSNa requires: 887.7510], which showed δ_H (500 MHz, CDCl₃): 7.60–7.54 (5H, m), 3.41 (2H, t, *J* 7.3 Hz), 3.34 (3H, s), 2.98–2.94 (1H, m), 1.84 (2H, br pent, *J* 7.5 Hz), 1.64–1.61 (1H, m), 1.48–1.22 (72H, m), 1.18–1.05 (4H, m), 0.89 (3H, t, *J* 7.0 Hz), 0.86 (3H, d, *J* 6.0 Hz), 0.68–0.62 (2H, m), 0.57 (1H, dt, *J* 4.1, 7.9 Hz), –0.32 (1H, br q, *J* 5.1 Hz); δ_C (125 MHz, CDCl₃): 154.0, 133.8, 130.0(–), 129.7(–), 123.9(–), 85.5(–), 57.7(–), 35.4(–), 33.4(+), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.1(+), 30.0(+), 29.9(+), 29.74(+), 29.7(+), 29.65(+), 29.4(+), 29.3(+), 29.1(+), 29.07(+), 28.7(+), 28.6(+), 27.6(+), 26.2(+), 22.7(+), 15.8(–), 15.7(–), 14.9(–), 14.1(–), 10.9(+); ν_{max}: 2926, 2851, 1509, 1464, 1097 cm^{–1}.

3.1.43. 5-{7-[(1*R*,2*S*)-2-((17*S*,18*S*)-17-Methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (47**).** (1*R*,2*S*)-1-(7-Bromoheptyl)-2-((17*S*,18*S*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (7.0 g, 9.13 mmol) in tetrahydrofuran (25 mL) was added to a stirred solution of 1-phenyl-1*H*-tetrazol-5-thiol (1.72 g, 9.65 mmol) and potassium carbonate (4.8 g, 34.7 mmol) in acetone (75 mL) at room temperature. The mixture was stirred for 5 h at 40 °C, then at room temperature for 16 h, then worked up and purified as before to give 5-{7-[(1*R*,2*S*)-2-((17*S*,18*S*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (**47**) as a slightly off white solid (7.65 g, 97%) {[α]_D²²–5.11 (c 1.31, CHCl₃)}, which showed an identical NMR spectrum to that above.

3.1.44. Butyric acid (1*R*,2*S*)-2-(1-phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)cyclopropyl methyl ester (49**).** Diethyl azodicarboxylate (12.2 g, 70 mmol) in tetrahydrofuran (20 mL) was added to a stirred solution of (1*R*,2*S*)-1-butryloxymethyl-2-hydroxymethylcyclopropane (**48**)³⁹ (6.9 g, 40 mmol), triphenylphosphine (15.3 g, 58.3 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (9.7 g, 54.4 mmol) in tetrahydrofuran (120 mL) maintaining the temperature at 0–5 °C throughout the addition. After 18 h at room temperature, the solvent was evaporated and the residue was treated with petrol/ether (5:2, 150 mL), stirred at room temperature for 45 min then filtered and the filter cake was washed with petrol/ether. The filtrate was evaporated to give a brown oil, which was purified by chromatography on silica eluting with 5:2 petrol/ether to give butyric acid (1*R*,2*S*)-2-(1-phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)cyclopropylmethyl ester (**49**) as a slightly yellow viscous oil (11.32 g, 85%) {[α]_D²⁴–1.2 (c 1.06, CHCl₃)} [found [M+Na]⁺: 355.1185; C₁₆H₂₀N₄NaO₂S requires: 355.1199], which showed δ_H (500 MHz, CDCl₃): 7.60–7.53 (5H, m), 4.34 (1H, dd, *J* 6.6, 12.3 Hz), 3.96 (1H, dd, *J* 9.2, 12.0 Hz), 3.59 (1H, dd, *J* 7.9, 13.5 Hz), 3.43 (1H, dd, *J* 7.9, 13.5 Hz), 2.27 (2H, t, *J* 7.6 Hz), 1.64 (2H, sext, *J* 7.6 Hz), 1.51 (1H, d pent, *J* 5.7, 8.0 Hz),

1.43–1.36 (1H, m), 0.97 (1H, dt, J 5.4, 8.2 Hz), 0.93 (3H, t, J 7.3 Hz), 0.40 (1H, q, J 5.7 Hz); δ_C (125 MHz, $CDCl_3$): 173.5, 154.3, 133.8, 130.1(+), 129.7(+), 123.8(+), 63.7(–), 36.2(–), 34.2(–), 18.4(–), 16.4(+), 15.5(+), 13.6(+), 11.0(–); ν_{max} : 2965, 2875, 1732, 1500, 1174, 983, 763 cm^{-1} .

3.1.45. Butyric acid (1*R*,2*S*)-2-(1-phenyl-1*H*-tetrazol-5-sulfonylmethyl)cyclopropyl methyl ester (50). A solution of ammonium heptamolybdate(VI) tetrahydrate (18.59 g, 15.06 mmol) in ice cold H_2O_2 (35% w/w, 50 mL) was added with stirring to butyric acid (1*R*,2*S*)-2-(1-phenyl-1*H*-tetrazol-5-ylsulfanylmethyl)cyclopropylmethyl ester (49) (10.00 g, 30.12 mmol) in tetrahydrofuran (125 mL) and IMS (250 mL) at 10 °C and stirred at rt for 2 h. A further solution of heptamolybdate (5.03 g, 4.07 mmol) in ice cold H_2O_2 (35% w/w, 15 mL) was added and the mixture was stirred for 19 h, then poured into water (1.5 L) and extracted with dichloromethane (1×300 mL, 2×80 mL). The combined organic layers were washed with water (700 mL), dried and evaporated to give a residue, which was purified by chromatography on silica eluting with 2:1 petrol/ether to give a thick pale yellow oil, butyric acid (1*R*,2*S*)-2-(1-phenyl-1*H*-tetrazol-5-sulfonylmethyl)cyclopropylmethyl ester (50) (10.18 g, 93%) [found $[M+Na]^+$: 387.1079; $C_{16}H_{20}N_4O_4SNa$ requires: 387.1097] $\{[\alpha]_D^{24} +52.7$ (c 1.45, $CHCl_3$)}, which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.69 (2H, m), 7.65–7.59 (3H, m), 4.37 (1H, dd, J 5.7, 12.0 Hz), 4.03 (1H, dd, J 5.4, 15.0 Hz), 3.92 (1H, dd, J 8.2, 12.0 Hz), 3.67 (1H, dd, J 8.9, 15.0 Hz), 2.31 (2H, t, J 7.6 Hz), 1.67 (2H, sext, J 7.6 Hz), 1.52–1.43 (2H, m), 1.03 (1H, dt, J 5.7, 8.5 Hz), 0.97 (3H, t, J 7.6 Hz), 0.60 (1H, q, J 5.7 Hz); δ_C (125 MHz, $CDCl_3$): 173.3, 153.7, 133.1, 131.5(+), 129.7(+), 125.2(+), 63.4(–), 56.8(–), 36.1(–), 18.4(–), 14.7(+), 13.6(+), 9.7(–), 8.7(+); ν_{max} : 2967, 1731, 1343, 1153, 765 cm^{-1} .

3.1.46. Butyric acid (1*R*,2*S*)-2-(7-bromoheptyl)cyclopropylmethyl ester (51). Lithium hexamethyldisilazide (33.68 mL, 35.7 mmol, 1.06 M) was added dropwise to a stirred solution of butyric acid (1*R*,2*S*)-2-(1-phenyl-1*H*-tetrazol-5-sulfonylmethyl)cyclopropyl methyl ester (50) (10.0 g, 27.46 mmol) and 6-bromohexanal (4.67 g, 26.09 mmol) in dry THF (130 mL) under nitrogen at –20 °C, allowed to reach room temperature and stirred for 16 h, then worked up as above to give butyric acid (1*R*,2*S*)-2-((*E/Z*)-7-bromohept-1-enyl)cyclopropylmethyl esters (2:1, *E/Z*) (6.44 g, 74%). 2,4,6-Triisopropylbenzene sulfonylhydrazide (14.88 g, 49.85 mmol) was added to a stirred solution of the esters (5.75 g, 18.12 mmol) in tetrahydrofuran (150 mL) and stirred at 50 °C for 20 h. Further hydrazide (3.7 g, 12.40 mmol) was added and the reaction mixture was stirred at 50 °C for 22 h then diluted with petrol/ether (1:1, 200 mL) and aq sodium hydroxide (100 mL, 2%). The aqueous layer was re-extracted with petrol/diethyl ether (1:1, 2×50 mL) and the combined organic layers were washed with water (100 mL), dried and evaporated. 1H NMR showed that there was still some starting material left. The hydrogenation was repeated as before to give a product, which was purified by chromatography on silica eluting with petrol/ether (10:1) to give butyric acid (1*R*,2*S*)-2-(7-bromoheptyl)cyclopropyl methyl ester (51) as a colourless oil (4.61 g, 80%) [found $[M+Na]^+$: 341.1021;

$C_{15}H_{27}Br^{79}NaO_2$ requires: 341.1087] $\{[\alpha]_D^{24} +10.03$ (c 1.50, $CHCl_3$)}, which showed spectroscopic data identical to those for its enantiomer 42 (see Supplementary data).

3.1.47. [(1*R*,2*S*)-2-(7-Bromoheptyl)cyclopropyl] methanol (52). [(1*R*,2*S*)-2-(7-Bromoheptyl)cyclopropyl]methanol (52) [found $[M+Na]^+$: 271.0623; $C_{11}H_{21}BrNaO$ requires: 271.0668] $\{[\alpha]_D^{24} +12.87$ (c 1.65, $CHCl_3$)} was prepared from butyric acid (1*R*,2*S*)-2-(7-bromoheptyl)cyclopropylmethyl ester (51) using the same method as for the enantiomer 43. The spectroscopic data were identical to those for 43 (see Supplementary data).

3.1.48. (1*R*,2*S*)-2-(7-Bromoheptyl)cyclopropane carbaldehyde (53). (1*R*,2*S*)-2-(7-Bromoheptyl)cyclopropane carbaldehyde (53) was prepared as a colourless oil (76%) [found $[M+Na]^+$: 269.0486; $C_{11}H_{19}BrNaO$ requires: 269.0511] $\{[\alpha]_D^{24} +8.19$ (c 1.28, $CHCl_3$)} from [(1*R*,2*S*)-2-(7-bromoheptyl)cyclopropyl]methanol (52) using the same method as described for the enantiomer 44. The spectroscopic data were identical to those for 44 (see Supplementary data).

3.1.49. (1*S*,2*R*)-1-(7-Bromoheptyl)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (54). Lithium hexamethyldisilazide (2.97 mL, 3.15 mmol, 1.06 M) was added dropwise to a stirred solution of (1*R*,2*S*)-2-(7-bromoheptyl)cyclopropane carbaldehyde (53) (0.5 g, 2.02 mmol) and 5-((16*R*,17*R*)-16-methoxy-17-methylpentatriacontan-1-sulfonyl)-1-phenyl-1*H*-tetrazole (36) (1.81 g, 2.42 mmol) in dry tetrahydrofuran (25 mL) under nitrogen at –15 °C. The mixture was allowed to reach room temperature and stirred for 2 h, then quenched with satd aq ammonium chloride (25 mL) and petrol/ether (1:1, 50 mL). The aqueous layer was re-extracted with petrol/ether (1:1, 2×25 mL). The combined organic layers were washed with brine (25 mL), dried and evaporated to give a pale yellow oil, which was purified by chromatography on silica eluting with petrol/ether (9:1) to give (1*S*,2*R*)-1-(7-bromoheptyl)-2-((*E/Z*)-17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (7:1) (1.14 g, 74%). Hydrogenation and purification as above gave (1*S*,2*R*)-1-(7-bromoheptyl)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (54) as a viscous colourless oil (0.92 g, 80%) $\{[\alpha]_D^{24} +5.17$ (c 1.44, $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$): 3.42 (2H, t, J 7.0 Hz), 3.35 (3H, s), 2.98–2.95 (1H, m), 1.87 (2H, pent, J 6.9 Hz), 1.66–1.6 (1H, m), 1.48–1.2 (72H, m), 1.18–1.06 (4H, m), 0.9 (3H, t, J 7.0 Hz), 0.87 (3H, d, J 7.0 Hz), 0.68–0.64 (2H, m), 0.57 (1H, dt, J 4.1, 7.9 Hz), –0.32 (1H, q, J 5.4 Hz); δ_C (125 MHz, $CDCl_3$): 85.5(–), 57.7(–), 35.4(–), 32.9(+), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.1(+), 30.0(+), 29.9(+), 29.7(+), 29.42(+), 29.4(+), 28.8(+), 28.7(+), 28.65(+), 28.2(+), 27.6(+), 26.2(+), 22.7(+), 15.8(–), 15.7(–), 14.9(–), 14.1(–), 10.9(+); ν_{max} : 2922, 1464, 1098, 720 cm^{-1} .

3.1.50. 5-{7-[(1*S*,2*R*)-2-((17*R*,18*R*)-17-Methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (55). (1*S*,2*R*)-1-(7-Bromoheptyl)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropane (54) (0.5 g, 0.65 mmol) in tetrahydrofuran (10 mL) was added to a stirred solution of 1-phenyl-1*H*-tetrazol-5-thiol (0.13 g, 0.73 mmol) and potassium carbonate (0.35 g,

2.53 mmol) in acetone (30 mL) at room temperature. The reaction mixture was stirred for 5 h at 40 °C, at room temperature for 16 h and then diluted with water (50 mL) and dichloromethane (100 mL). The aqueous layer was re-extracted with dichloromethane (2×25 mL). The combined organic layers were washed with brine (2×50 mL), dried and evaporated to give an oil, which solidified later. The crude product was purified by chromatography on silica eluting with petrol/ether (5:1) to give 5-{7-[(1*S*,2*R*)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (**55**) as a colourless viscous oil (0.5 g, 88%) [found $[M+Na]^+$: 887.7434; $C_{55}H_{100}N_4NaOS$ requires: 887.7510] $\{[\alpha]_D^{25} +4.44$ (c 1.07, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.61–7.54 (5H, m), 3.41 (2H, t, J 7.6 Hz), 3.35 (3H, s), 2.98–2.94 (1H, m), 1.83 (2H, pent, J 7.3 Hz), 1.65–1.61 (1H, m), 1.47–1.25 (72H, m), 1.17–1.08 (4H, m), 0.9 (3H, t, J 7.0 Hz), 0.87 (3H, d, J 7.0 Hz), 0.68–0.62 (2H, m), 0.57 (1H, dt, J 4.1, 8.2 Hz), –0.33 (1H, q, J 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 154.0, 133.8, 130.0(–), 129.8(–), 123.9(–), 85.5(–), 57.7(–), 35.4(–), 33.4(+), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.1(+), 30.0(+), 29.9(+), 29.8(+), 29.74(+), 29.7(+), 29.4(+), 29.3(+), 29.1(+), 29.07(+), 28.7(+), 28.6(+), 27.6(+), 26.2(+), 22.7(+), 15.8(–), 15.7(–), 14.9(–), 14.1(–), 10.9(+); ν_{max} : 2926, 2851, 1509, 1464, 1097 cm^{-1} .

3.1.51. 5-{7-[(1*R*,2*S*)-2-((17*R*,18*R*)-17-Methoxy-18-methylhexatriacontyl)cyclopropyl]heptane-1-sulfonyl}-1-phenyl-1*H*-tetrazole (56**).** A solution of ammonium heptamolybdate(VI) tetrahydrate (2.1 g, 1.7 mmol) in H_2O_2 (35% w/w, 6 mL) was added dropwise at 5 °C to a stirred solution of 5-{7-[1*R*,2*S*]-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (**46**) (2.9 g, 3.35 mmol) in methylated spirit (40 mL) and tetrahydrofuran (40 mL). The resulting yellow solution was stirred for 1 h then three more identical solutions of heptamolybdate in H_2O_2 were added over 1 h. The reaction mixture was stirred at room temperature for 16 h and then diluted with water (100 mL) and dichloromethane (50 mL). The aqueous layer was re-extracted with dichloromethane (2×50 mL). The combined organic layers were washed with water, brine, dried and evaporated to give the crude product. Chromatography on silica eluting with petrol/ether (10:2) gave 5-{7-[(1*R*,2*S*)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptane-1-sulfonyl}-1-phenyl-1*H*-tetrazole (**56**) as a white solid (2.19 g, 73%), mp 37–39 °C $\{[\alpha]_D^{22} +4.13$ (c 1.92, $CHCl_3$) [found $[M+Na]^+$: 919.7435; $C_{55}H_{100}N_4O_3SNa$ requires: 919.7408], which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.69 (2H, br dd, J 1.3, 7.9 Hz), 7.63–7.57 (3H, m), 3.74 (2H, distorted t, J 8.2 Hz), 3.35 (3H, s), 2.98–2.95 (1H, br pent, J 4.1 Hz), 1.97 (2H, br pent, J 7.6 Hz), 1.65–1.62 (1H, m), 1.52 (2H, br pent, J 7.6 Hz), 1.48–1.22 (70H, m), 1.17–1.05 (4H, m), 0.89 (3H, t, J 7.0 Hz), 0.86 (3H, d, J 7.0 Hz), 0.69–0.65 (2H, m), 0.58 (1H, dt, J 3.8, 8.0 Hz), –0.32 (1H, br q, J 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 153.5, 133.1, 131.4(–), 129.7(–), 125.1(–), 85.4(–), 57.7(–), 56.1(+), 35.4(–), 32.4, 31.9(+), 30.5(+), 30.2(+), 30.0(+), 29.9(+), 29.74(+), 29.7(+), 29.6(+), 29.4(+), 29.1(+), 28.9(+), 28.7(+), 28.6(+), 28.1(+), 27.6(+), 26.2(+), 22.7(+), 21.9(+), 15.8(–), 15.7(–), 14.9(–), 14.1(–), 10.9(+); ν_{max} : 2908, 1596, 1499, 1464, 1343, 1153, 1099, 760 cm^{-1} .

3.1.52. 5-{7-[(1*R*,2*S*)-2-((17*S*,18*S*)-17-Methoxy-18-methylhexatriacontyl)cyclopropyl]heptane-1-sulfonyl}-1-phenyl-1*H*-tetrazole (69**).** A solution of ammonium heptamolybdate(VI) tetrahydrate (4.8 g, 3.88 mmol) in 35% H_2O_2 (w/w) (13 mL) was added dropwise at 5 °C to a stirred solution of 5-{7-[1*R*,2*S*]-2-((17*S*,18*S*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfanyl}-1-phenyl-1*H*-tetrazole (**47**) (7.5 g, 8.66 mmol) in methylated spirit (120 mL) and tetrahydrofuran (120 mL). The resulting yellow solution was stirred for 1 h then three more identical solutions of ammonium heptamolybdate(VI) tetrahydrate in 35% H_2O_2 (w/w) were added over 1 h. The mixture was stirred at room temperature for 16 h, then worked up and purified as above to give 5-{7-[(1*R*,2*S*)-2-((17*S*,18*S*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptane-1-sulfonyl}-1-phenyl-1*H*-tetrazole (**69**) as a white solid (6.53 g, 84%) $\{[\alpha]_D^{22} -4.81$ (c 1.391, $CHCl_3$), which showed an identical NMR spectrum to that above.

3.1.53. (R)-2-[(R)-1-Acetoxy-18-[(1*R*,2*S*)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (58**).** Lithium hexamethyldisilazide (0.76 mL, 0.767 mmol, 1 M) was added dropwise to a stirred solution of ((1*R*,2*R*)-1-acetoxy-11-oxoundecyl)hexacosanoic acid methyl ester (**57**) (0.25 g, 0.393 mmol)³¹ and 5-{7-[1*R*,2*S*]-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptane-1-sulfonyl}-1-phenyl-1*H*-tetrazole (**56**) (0.52 g, 0.59 mmol) in dry THF (15 mL) under nitrogen at –12 °C. The reaction was exothermic and the temperature rose to –5 °C resulting in a dark orange solution. The mixture was allowed to reach room temperature and stirred for 2 h, cooled to 0 °C and quenched with satd aq ammonium chloride (5 mL). The product was extracted with petrol/ether (2×50 mL), dried and evaporated to give a thick oil, which was purified by chromatography on silica eluting with petrol/ether (5:0.5) to give (R)-2-[(*E/Z*)-(R)-1-acetoxy-18-[(1*R*,2*S*)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadec-11-enyl]hexacosanoic acid methyl ester (2.5:1) (0.35 g, 68%) as a thick colourless oil, which showed δ_H (500 MHz, $CDCl_3$) (major isomer): 5.40–5.38 (2H, br m), 5.09 (1H, br dt, J 4.0, 8.0 Hz), 3.68 (3H, s), 3.34 (3H, s), 2.98–2.94 (1H, m), 2.62 (1H, ddd, J 4.5, 7.0, 10.8 Hz), 2.03 (3H, s), 1.97 (3H, br s), 1.64–1.59 (2H, m), 1.55–1.52 (1H, m), 1.46–1.22 (133H, br m), 1.17–1.05 (4H, m), 0.88 (6H, t, J 7.0 Hz), 0.85 (3H, d, J 7.0 Hz), 0.68–0.64 (2H, br m), 0.57 (1H, br dt, J 4.1, 8.2 Hz), –0.33 (1H, br q, J 5.1 Hz); minor isomer: 5.35 (2H, br m), the remaining signals were obscured by the major isomer; δ_C (125 MHz, $CDCl_3$) (for the mixture): 173.6, 170.3, 130.4, 130.3, 129.91, 129.9, 85.4, 74.1, 57.7, 51.5, 49.6, 35.6, 35.3, 32.6, 32.4, 31.9, 31.7, 30.5, 30.23, 30.2, 30.0, 29.9, 29.8, 29.7 (v br), 29.66, 29.63, 29.6, 29.52, 29.5, 29.44, 29.4, 29.36, 29.3, 29.23, 29.2, 28.72, 28.7, 28.1, 27.6, 27.5, 27.2, 26.2, 25.0, 22.7, 21.0, 15.8, 14.9, 14.1, 10.9. Dipotassium azodicarboxylate (1.5 g, 8.04 mmol) was added with stirring to the above methyl esters (0.35 g, 0.268 mmol) in dry THF (10 mL) and methanol (5 mL) at 10 °C under nitrogen, resulting in a yellow suspension. A solution of glacial acetic acid (2 mL) in dry THF (4 mL) was added dropwise over 16 h, after which a white precipitate had formed. The mixture was cooled to 0 °C and poured slowly into satd aq ammonium chloride (5 mL). The product was extracted

with petrol/ether (1:1, 3×30 mL). The combined organic layers were washed with water (20 mL), dried and evaporated to give a thick oil, which solidified slowly; however, the ¹H NMR spectra showed that there was still starting material left. The procedure was repeated twice for another 24 h and the residue was purified by chromatography on silica eluting with petrol/ether (5:1) (*R_f*=0.5) to give (*R*)-2-[(*R*)-1-acetoxy-18-[(1*R*,2*S*)-2-[(17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl]cyclopropyl]octadecyl]hexacosanoic acid methyl ester (**58**) as a semi solid (0.29 g, 83%) [$[\alpha]_D^{22} +7.17$ (*c* 1.32, CHCl₃)] [found [M+Na]⁺: 1332.3147; C₈₈H₁₇₂O₅Na requires: 1332.3097]; δ_H (500 MHz, CDCl₃): 5.09 (1H, br dt, *J* 4.1, 8.2 Hz), 3.68 (3H, s), 3.34 (3H, s), 2.97–2.94 (1H, m), 2.62 (1H, ddd, *J* 4.5, 7, 10.8 Hz), 2.03 (3H, s), 1.68–1.58 (4H, m), 1.56–1.48 (1H, m), 1.46–1.22 (138H, br m), 1.18–1.05 (4H, m), 0.89 (6H, t, *J* 6.6 Hz), 0.85 (3H, d, *J* 6.9 Hz), 0.69–0.63 (2H, m), 0.56 (1H, dt, *J* 3.8, 8.0 Hz), –0.33 (1H, br q, *J* 4.8 Hz); δ_C (125 MHz, CDCl₃): 173.6, 170.3, 85.4(–), 74.1(–), 57.7(–), 51.5(–), 49.6(–), 35.3(–), 32.4(+), 31.9(+), 31.7(+), 30.5(+), 30.2(+), 30.0(+), 29.9(+), 29.7(+), 29.6(+), 29.5(+), 29.43(+), 29.4(+), 29.35(+), 28.7(+), 28.1(+), 27.6(+), 27.5(+), 26.2(+), 25.0(+), 22.7(+), 21.0(–), 15.8(–), 14.9(–), 14.1(–), 10.9(+); ν_{max} : 2920, 1743, 1469, 1375, 1237, 1162, 719 cm^{–1}.

3.1.54. (*E*)-13-(2,2-Dimethylpropionyloxy)tridec-2-enoic acid methyl ester (63**).** (Methoxycarbonylmethylene)triphenylphosphorane (43.25 g, 0.127 mol) was added to a stirred solution of 2,2-dimethylpropionic acid 11-oxoundecyl ester (see Supplementary data) (30.00 g, 0.111 mol) in toluene (500 mL). After 16 h at room temperature, the toluene was evaporated to give a residue, which was diluted with petrol/ether (5:2, 500 mL) and refluxed for 30 min. The solid was filtered off and washed with petrol/ether (150 mL). The filtrate was evaporated to give a residue, which was again diluted with petrol/ether (5:2, 500 mL) and refluxed for 30 min. The solid was filtered off and washed with petrol/ether (5:2) and then the filtrate was evaporated. Chromatography on silica eluting with petrol/ether (5:2) gave a colourless oil, (*E*)-13-(2,2-dimethylpropionyloxy)tridec-2-enoic acid methyl ester (**63**) (31 g, 85%) [found [M+Na]⁺: 349.2339; C₁₉H₃₄NaO₄ requires: 349.2349], which showed δ_H (500 MHz, CDCl₃): 6.97 (1H, dt, *J* 7.0, 15.5 Hz), 5.81 (1H, td, *J* 1.6, 15.5 Hz), 4.04 (2H, t, *J* 6.6 Hz), 3.72 (3H, s), 2.19 (2H, dq, *J* 1.3, 7.6 Hz), 1.61 (2H, pent, *J* 6.6 Hz), 1.45 (2H, pent, *J* 6.6 Hz), 1.37–1.25 (12H, m), 1.19 (9H, s); δ_C (125 MHz, CDCl₃): 178.6, 167.2, 149.7(+), 120.8(+), 64.4(–), 51.3(+), 38.7, 32.2(–), 29.42(–), 29.4(–), 29.3(–), 29.2(–), 29.1(–), 28.6(–), 28.0(–), 27.2(+), 25.9(–); ν_{max} : 2928, 2855, 1729, 1158 cm^{–1}.

3.1.55. (2*S*,3*R*)-13-(2,2-Dimethylpropionyloxy)-2,3-dihydroxytridecanoic acid methyl ester (64**).** The (DHQD)₂PHAL ligand (0.55 g, 0.70 mmol, 0.01 mol equiv), K₃Fe(CN)₆ (69.27 g, 0.21 mol, 3 mol equiv), K₂CO₃ (29.08 g, 0.21 mol, 3 mol equiv) and OsO₄ (2.8 mL, 2.81 mmol, 0.04 mol equiv; 2.5 wt % solution in 2-methyl-2-propanol) were dissolved in 1:1 water and 2-methyl-2-propanol (800 mL) at room temperature. Then MeSO₂NH₂ (6.67 g, 0.07 mol, 1 mol equiv) was added and the mixture was cooled to 2 °C while being vigorously stirred. (*E*)-13-(2,2-Dimethylpropionyloxy)tridec-2-enoic acid methyl ester

(**63**) (23 g, 0.07 mol) was added at 2 °C. The reaction mixture was stirred at 2–4 °C for 8 h. When TLC showed no starting material, sodium metabisulfite (20 g, 0.105 mol) was added carefully. The mixture was allowed to reach room temperature and stirred for 45 min, then extracted with dichloromethane (3×500 mL), dried and evaporated. Chromatography on silica eluting with petrol/ethyl acetate (5:1, then 1:1) gave (2*S*,3*R*)-13-(2,2-dimethylpropionyloxy)-2,3-dihydroxytridecanoic acid methyl ester (**64**) as a colourless oil (24.74 g, 97%) [found [M+Na]⁺: 383.2395; C₁₉H₃₆NaO₆ requires: 383.2404] [$[\alpha]_D^{24} +11.1$ (*c* 1.03, CHCl₃)], which showed δ_H (500 MHz, CDCl₃): 4.10 (1H, br d, *J* 2 Hz), 4.04 (2H, t, *J* 6.6 Hz), 3.89 (1H, br dt, *J* 2.0, 7.6 Hz), 3.82 (3H, s), 3.08 (1H, br s), 2.04 (1H, br s), 1.61 (4H, br pent, *J* 6.6 Hz), 1.50–1.43 (1H, m), 1.38–1.26 (13H, m), 1.19 (9H, s); δ_C (125 MHz, CDCl₃): 178.7, 174.1, 73.1(+), 72.7(+), 64.4(–), 52.8(+), 38.7, 33.7(–), 29.5(–), 29.43(–), 29.4(–), 29.2(–), 28.6(–), 27.2(+), 25.9(–), 25.7(–); ν_{max} : 3449, 2930, 2855, 1729 cm^{–1}.

3.1.56. (2*S*,3*R*)-5-[10-(2,2-Dimethylpropionyloxy)decyl]-2,2-dioxo-2λ⁶-[1,3,2]-dioxathiolane-4-carboxylic acid methyl ester (64**).** (2*S*,3*R*)-13-(2,2-Dimethylpropionyloxy)-2,3-dihydroxytridecanoic acid methyl ester (**64**) (24.5 g, 68.1 mmol) was dissolved in CCl₄ (120 mL). Thionyl chloride (10.9 mL, 149.72 mmol, 2.2 mol equiv) was added and the mixture was vigorously refluxed for 2 h. After cooling, the solution was carefully diluted with CH₃CN (120 mL), followed by the addition of ruthenium trichloride hydrate (1.41 g, 6.8 mmol, 0.1 mol equiv) and NaIO₄ (36.4 g, 170.13 mmol, 2.5 mol equiv) and then water (240 mL) was added dropwise at first and then slowly. The mixture was stirred overnight and then poured into ether (600 mL). The organic layer was separated and the aqueous layer was re-extracted with ether (2×200 mL). The combined organic layers were washed with water (100 mL), satd aq sodium bicarbonate (100 mL) and brine (100 mL), then dried and evaporated to give a dark residue. Sodium thiosulfate pentahydrate was added to remove the iodine and the mixture was extracted with dichloromethane (2×200 mL). The organic layer was dried and evaporated to give a very dark residue; chromatography on silica eluting with petrol/ether (1:1) gave a colourless oil, (2*S*,3*R*)-5-[10-(2,2-dimethylpropionyloxy)decyl]-2,2-dioxo-2λ⁶-[1,3,2]-dioxathiolane-4-carboxylic acid methyl ester (26.75 g, 93%) [found [M+Na]⁺: 445.1857; C₁₉H₃₄NaO₈S requires: 445.1867] [$[\alpha]_D^{24} +32.76$ (*c* 1.23, CHCl₃)], which showed δ_H (500 MHz, CDCl₃): 4.95 (1H, td, *J* 5.1, 7.3 Hz), 4.89 (1H, br d, *J* 7.3 Hz), 4.05 (2H, t, *J* 6.6 Hz), 3.90 (3H, s), 2.01–1.96 (2H, m), 1.62 (2H, br pent, *J* 6.6 Hz), 1.57–1.45 (2H, m), 1.39–1.26 (12H, m), 1.20 (9H, s); δ_C (125 MHz, CDCl₃): 178.6, 165.4, 84.1(+), 79.8(+), 64.4(–), 53.7(+), 38.7, 33.0(–), 29.4(–), 29.3(–), 29.2(–), 29.1(–), 28.8(–), 28.6(–), 27.2(+), 25.8(–), 24.8(–); ν_{max} : 2930, 2856, 1774, 1724 cm^{–1}.

3.1.57. (*R*)-13-(2,2-Dimethylpropionyloxy)-3-hydroxytridecanoic acid methyl ester (65**).** (2*S*,3*R*)-5-[10-(2,2-Dimethylpropionyloxy)decyl]-2,2-dioxo-2λ⁶-[1,3,2]-dioxathiolane-4-carboxylic acid methyl ester (22 g, 51.88 mmol) was dissolved in *N,N*-dimethylacetamide (300 mL) and NaBH₄ (2.26 g, 59.67 mmol, 1.15 mol equiv) was slowly added at 0 °C. The mixture was stirred at room temperature for 1 h

and then the solvent was distilled under high vacuum. The residue was diluted with tetrahydrofuran (250 mL) and then water (0.5 mL) and concentrated sulfuric acid (2 mL) were added. The mixture was stirred for 4 h until a clear solution was obtained followed by the addition of sodium metabisulfite (25 g) and the mixture was stirred for another 30 min. It was then filtered through a pad of silica and washed with tetrahydrofuran. The filtrate was evaporated to give a residue, which was purified by chromatography on silica eluting with petrol/ethyl acetate (10:3) gave (*R*)-13-(2,2-dimethylpropionyloxy)-3-hydroxytridecanoic acid methyl ester (**65**) (12.14 g, 68%) [found $[M+Na]^+$: 367.2427; $C_{19}H_{36}NaO_5$ requires: 367.2455] $\{[\alpha]_D^{26} -10$ (*c* 1.23, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.6 Hz), 4.01–3.97 (1H, m), 3.71 (3H, s), 2.51 (1H, dd, *J* 3.2, 16.4 Hz), 2.41 (1H, dd, *J* 9.2, 16.4 Hz), 1.61 (2H, pent, *J* 6.6 Hz), 1.55–1.50 (1H, m), 1.44–1.38 (2H, m), 1.36–1.25 (14H, m), 1.19 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.6, 173.4, 68.0(+), 64.4(–), 51.7(+), 41.1(–), 38.7, 36.5(–), 29.5(–), 29.44(–), 29.42(–), 29.4(–), 29.2(–), 28.6(–), 27.2(+), 25.8(–), 25.4(–); ν_{max} : 3517, 2922, 2854, 1732 cm^{-1} .

3.1.58. (2*R*,3*R*)-2-Allyl-[11-(2,2-dimethylpropionyloxy)-1-hydroxyundecyl]pent-4-enoic acid methyl ester. Butyllithium (3.05 mL, 6.40 mmol, 2.2 mol equiv) was added to a stirred solution of diisopropylamine (0.65 g, 6.40 mmol, 2.2 mol equiv) in dry THF (40 mL) under nitrogen at $-78^\circ C$. The mixture was allowed to reach room temperature and then cooled to $-78^\circ C$ before (*R*)-13-(2,2-dimethylpropionyloxy)-3-hydroxytridecanoic acid methyl ester (**65**) (1 g, 2.91 mmol) in dry THF (20 mL) was added dropwise. The mixture was allowed to slowly warm to $0^\circ C$ in the cooling bath over 2 h and then re-cooled to $-65^\circ C$ before allyl iodide (0.32 mL, 3.49 mmol, 1.2 mol equiv) and HMPA (1.01 mL, 5.81 mmol, 2 mol equiv) in dry THF (2 mL) were added dropwise. The mixture was allowed slowly to warm up to $-5^\circ C$ over 2 h. Ammonium chloride (10 mL) was added and extracted with ether/ethyl acetate (1:1, 3×50 mL). The combined organic layers were washed with brine (50 mL), dried and evaporated to give a residue, which was purified by chromatography on silica eluting with petrol/ethyl acetate (4:1) to give (*2R,3R*)-2-allyl-[11-(2,2-dimethylpropionyloxy)-1-hydroxyundecyl]pent-4-enoic acid methyl ester as a pale yellow oil (614 mg, 55%) [found $[M+Na]^+$: 407.2751; $C_{22}H_{40}NaO_5$ requires: 407.2768] $\{[\alpha]_D^{25} +1.94$ (*c* 1.19, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 5.75 (1H, br ddd, *J* 7.0, 10.0, 17.0 Hz), 5.10 (1H, br qd, *J* 1.0, 17.0 Hz), 5.04 (1H, br qd, *J* 1.0, 10.0 Hz), 4.04 (2H, t, *J* 6.7 Hz), 3.71 (3H, s), 3.70–3.66 (1H, m), 2.54 (1H, ddd, *J* 5.1, 6.3, 11.3 Hz), 2.49 (1H, br d, *J* 8.2 Hz), 2.47–2.37 (2H, m), 1.61 (2H, br pent, *J* 6.6 Hz), 1.50–1.40 (3H, m), 1.35–1.25 (13H, m), 1.19 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.6, 175.3, 134.9(+), 117.1(–), 71.7(+), 64.4(–), 51.5(+), 50.6(+), 38.7, 35.5(–), 33.8(–), 29.5(–), 29.44(–), 29.40(–), 29.2(–), 28.6(–), 27.2(+), 25.9(–), 25.7(–); ν_{max} : 3524, 2930, 2854, 1736, 1642 cm^{-1} .

3.1.59. (2*R*,3*R*)-2-Allyl-3-(*tert*-butyldimethylsilyloxy)-13-(2,2-dimethylpropionyloxy)tridecanoic acid methyl ester (66**).** Imidazole (0.95 g, 14.06 mmol) was added to a stirred solution of (*2R,3R*)-2-allyl-[11-(2,2-dimethyl-

propionyloxy)-1-hydroxyundecyl]pent-4-enoic acid methyl ester (3.6 g, 9.375 mmol) in dry DMF (40 mL) at room temperature. The reaction mixture was stirred for 15 min followed by the addition of *tert*-butyldimethylsilylchloride (1.83 g, 12.18 mmol) in DMF (10 mL) at $10^\circ C$ under a nitrogen atmosphere. The reaction mixture was allowed to reach room temperature and stirred for 16 h. When TLC showed that no starting material was left, the solvent was removed under high vacuum and the residue was diluted with dichloromethane (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×50 mL). The combined organic layers were washed with brine, dried and evaporated to give a pale yellow oily residue, which was purified by chromatography on silica eluting with petrol/ether (5:1) to give (*2R,3R*)-2-allyl-3-(*tert*-butyldimethylsilyloxy)-13-(2,2-dimethylpropionyloxy)tridecanoic acid methyl ester (**66**) as a colourless oil (4.23 g, 91%) [found $[M+Na]^+$: 521.3604; $C_{28}H_{54}O_5SiNa$ requires: 521.3633] $\{[\alpha]_D^{24} -12.34$ (*c* 1.32, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 5.74 (1H, tdd, *J* 7.0, 10.1, 17.0 Hz), 5.05 (1H, br dd, *J* 1.9, 17.0 Hz), 4.98 (1H, br dd, *J* 1.9, 10.1 Hz), 4.04 (2H, t, *J* 6.6 Hz), 3.94 (1H, br qd, *J* 1.6, 6.0 Hz), 3.65 (3H, s), 2.62 (1H, br ddd, *J* 4.5, 6.3, 10.8 Hz), 2.36–2.31 (1H, m), 2.26–2.1 (1H, m), 1.61 (2H, pent, *J* 6.9 Hz), 1.51–1.40 (4H, m), 1.37–1.25 (12H, m), 1.19 (9H, s), 0.87 (9H, s), -0.05 (3H, s), -0.03 (3H, s); δ_C (125 MHz, $CDCl_3$): 178.6, 174.0, 135.9(+), 116.3(–), 72.8(+), 64.4(–), 51.32(+), 51.3(+), 38.7, 33.6(–), 31.6(–), 29.7(–), 29.5(–), 29.46(–), 29.2(–), 28.6(–), 27.2(+), 25.9(–), 25.7(+), 24.1(–), 18.0, -4.4 (+), -4.9 (+); ν_{max} : 2930, 2856, 1732, 1462, 1158 cm^{-1} .

3.1.60. (2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-13-(2,2-dimethylpropionyloxy)-2-(2-oxoethyl)tridecanoic acid methyl ester. Lutidine (1.51 g, 14.05 mmol) was added to a stirred solution of (*2R,3R*)-2-allyl-3-(*tert*-butyldimethylsilyloxy)-13-(2,2-dimethylpropionyloxy)tridecanoic acid methyl ester (**66**) (3.5 g, 7.03 mmol) in dioxane/water (3:1, 100 mL) followed by the addition of osmium tetroxide (1.4 mL, 0.14 mmol, 2.5% w/w in 2-methyl-2-propanol) at room temperature. The mixture was stirred for 5 min and then sodium metaperiodate (6.03 g, 28.1 mmol) was added. After 2 h stirring, TLC showed that no starting material was left. The reaction mixture was diluted with dichloromethane (100 mL) and the organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×50 mL). The combined organic layers were washed with brine, dried and evaporated to give a crude product. Chromatography on silica eluting with petrol/ether (5:2) gave (*2R,3R*)-3-(*tert*-butyldimethylsilyloxy)-13-(2,2-dimethylpropionyloxy)-2-(2-oxoethyl)tridecanoic acid methyl ester as a pale yellow oil (3.34 g, 93%) [found $[M+Na]^+$: 523.3415; $C_{27}H_{52}O_6SiNa$ requires: 523.3425], which showed δ_H (500 MHz, $CDCl_3$): 9.8 (1H, br s), 4.05–4.02 (3H, including t, *J* 6.6 Hz), 3.68 (3H, s), 3.19 (1H, br td, *J* 3.8, 10.4 Hz), 2.96 (1H, br dd, *J* 10.5, 18.3 Hz), 2.68 (1H, dd, *J* 3.5, 18.3 Hz), 1.61 (2H, pent, *J* 6.6 Hz), 1.41–1.25 (16H, m), 1.19 (9H, s), -0.072 (3H, s), -0.064 (3H, s); δ_C (125 MHz, $CDCl_3$): 200.6(+), 178.6, 172.6, 71.8(+), 67.1(–), 64.4(–), 51.9(+), 45.3(+), 40.0(–), 38.7, 33.6(–), 29.5(–), 29.4(–), 29.2(–), 28.6(–), 27.2(+), 25.9(–), 25.7(+), 17.9, -4.6 (+), -4.7 (+).

3.1.61. (R)-2-[(R)-1-(tert-Butyldimethylsilyloxy)-11-(2,2-dimethylpropionyloxy)undecyl]hexacosanoic acid methyl ester (67). Lithium hexamethyldisilazide (8.33 mL, 8.83 mmol, 1.06 M) was added dropwise to a stirred solution of (2*R*,3*R*)-3-(tert-butyldimethylsilyloxy)-13-(2,2-dimethylpropionyloxy)-2-(2-oxoethyl)tridecanoic acid methyl ester (2.9 g, 5.66 mmol) and 5-(docosan-1-sulfonyl)-1-phenyl-1*H*-tetrazole⁴² (3.52 g, 6.79 mmol) in dry THF (50 mL) under nitrogen at -10°C . The mixture was allowed to reach room temperature and stirred for 3 h. When TLC showed that no starting material was left, it was worked up and purified as before to give (*E/Z*)-(*R*)-2-[(*R*)-1-(tert-butyl-dimethylsilyloxy)-11-(2,2-dimethylpropionyloxy)undecyl]-hexacos-4-enoic acid methyl ester (2.7:1) (3.73 g, 83%). Palladium on carbon (10%) (1.0 g) was added to a stirred solution of the esters (3.7 g, 4.67 mmol) in ethyl acetate (50 mL) and ethanol (50 mL) under hydrogen. When no further hydrogen was absorbed, the mixture was filtered through Celite and washed with ethyl acetate. The filtrate was evaporated to give a residue, which was purified by chromatography (petrol/ether, 10:1) to give (*R*)-2-[(*R*)-1-(tert-butyl-dimethylsilyloxy)-11-(2,2-dimethylpropionyloxy)undecyl]hexacosanoic acid methyl ester (**67**) as colourless oil (3.24 g, 87.3%) [found $[\text{M}+\text{Na}^+]$: 817.6986; $\text{C}_{49}\text{H}_{98}\text{O}_5\text{SiNa}$ requires: 817.7076] $\{[\alpha]_{\text{D}}^{25} -3.84$ (c 1.38, CHCl_3)}, which showed δ_{H} (500 MHz, CDCl_3): 4.05 (2H, t, J 6.6 Hz), 3.92–3.89 (1H, m), 3.65 (3H, s), 2.55–2.51 (1H, m), 1.63–1.24 (64H, m), 1.20 (9H, s), 0.88 (3H, t, J 7.0 Hz), 0.87 (9H, s), 0.048 (3H, s), 0.025 (3H, s); δ_{C} (125 MHz, CDCl_3): 178.6, 175.1, 73.2(–), 64.4(+), 51.6(–), 51.2(–), 38.7, 33.7(+), 31.9(+), 29.8(+), 29.7(+), 29.64(+), 29.6(+), 29.54(+), 29.5(+), 29.4(+), 29.3(+), 29.2(+), 28.6(+), 27.8(+), 27.5(+), 27.2(–), 25.9(+), 25.8, 25.75(–), 23.8(+), 22.7(+), 18.0, 14.1(–), -4.4 (–), -4.9 (–); ν_{max} : 2923, 2853, 1732, 1458, 1158 cm^{-1} .

3.1.62. (R)-2-[(R)-1-(tert-Butyldimethylsilyloxy)-11-hydroxyundecyl]hexacosanoic acid methyl ester. (*R*)-2-[(*R*)-1-(tert-Butyldimethylsilyloxy)-11-(2,2-dimethylpropionyloxy)undecyl]hexacosanoic acid methyl ester (**67**) (2.9 g, 3.65 mmol) in tetrahydrofuran (10 mL) was added to a stirred solution of potassium hydroxide (3.07 g, 54.7 mmol) in tetrahydrofuran/methanol/water (150 mL, 10:10:1). The mixture was refluxed at 70°C . After 3 h, TLC showed that no starting material was left and the mixture was quenched with water (25 mL) and extracted with ethyl acetate (3×75 mL). The combined organic layers were dried and evaporated to give a residue, which was purified by chromatography on silica eluting with petrol/ether (5:2) to give (*R*)-2-[(*R*)-1-(tert-butyl-dimethylsilyloxy)-11-hydroxyundecyl]hexacosanoic acid methyl ester as a colourless thick oil (2.07 g, 80%) [found $[\text{M}+\text{Na}^+]$: 733.6477; $\text{C}_{44}\text{H}_{90}\text{O}_4\text{SiNa}$ requires: 733.6501] $\{[\alpha]_{\text{D}}^{25} -4.45$ (c 1.01, CHCl_3)}, which showed δ_{H} (500 MHz, CDCl_3): 3.92–3.89 (1H, m), 3.66 (3H, s), 3.64 (2H, t, J 6.6 Hz), 2.53 (1H, ddd, J 10.7, 7.0, 3.6 Hz), 1.62–1.21 (65H, m), 0.88 (3H, t, J 7.0 Hz), 0.87 (9H, s), 0.052 (3H, s), 0.028 (3H, s); δ_{C} (125 MHz, CDCl_3): 175.1, 73.2(–), 63.1(+), 51.6(–), 51.2(–), 33.7(+), 32.8(+), 31.9(+), 29.8(+), 29.7(+), 29.64(+), 29.6(+), 29.55(+), 29.54(+), 29.5(+), 29.45(+), 29.4(+), 29.3(+), 27.9(+), 27.5(+), 25.8(–), 25.7(+), 23.8(+), 22.7(+), 18.0, 14.1(–), -4.4 (–), -4.9 (–); ν_{max} : 3356, 2925, 2853, 1741, 1464 cm^{-1} .

3.1.63. (R)-2-[(R)-1-(tert-Butyldimethylsilyloxy)-11-oxoundecyl]hexacosanoic acid methyl ester (68). (*R*)-2-[(*R*)-1-(tert-Butyldimethylsilyloxy)-11-hydroxyundecyl]hexacosanoic acid methyl ester (0.5 g, 0.774 mmol) in dichloromethane (10 mL) was added to a stirred suspension of pyridinium chlorochromate (0.42 g, 1.93 mmol) in dichloromethane (20 mL) at room temperature. The mixture was stirred vigorously for 3 h; when TLC showed no starting material, the mixture was diluted with ether (50 mL) and filtered through a pad of silica and Celite, washed with ether and the filtrate evaporated to give a residue. This was purified by chromatography on silica eluting with petrol/ether (5:2) to give (*R*)-2-[(*R*)-1-(tert-butyl-dimethylsilyloxy)-11-oxoundecyl]hexacosanoic acid methyl ester as a colourless oil (**68**) (0.46 g, 84%) [found $[\text{M}+\text{Na}^+]$: 731.6306; $\text{C}_{44}\text{H}_{88}\text{O}_4\text{SiNa}$ requires: 731.6344] $\{[\alpha]_{\text{D}}^{25} -4.48$ (c 1.38, CHCl_3)}, which showed δ_{H} (500 MHz, CDCl_3): 9.77 (1H, t, J 1.9 Hz), 3.92–3.89 (1H, m), 3.66 (3H, s), 2.52 (1H, ddd, J 11.0, 7.0, 3.8 Hz), 2.42 (2H, dt, J 1.9, 7.6 Hz), 1.63 (2H, pent, J 6.3 Hz), 1.55–1.22 (60H, m), 0.88 (3H, t, J 7 Hz), 0.87 (9H, s), 0.05 (3H, s), 0.027 (3H, s); δ_{C} (125 MHz, CDCl_3): 202.8(–), 175.1, 73.2(–), 51.6(–), 51.2(–), 43.9(+), 33.7(+), 31.9(+), 29.8(+), 29.7(+), 29.65(+), 29.6(+), 29.5(+), 29.4(+), 29.35(+), 29.3(+), 29.2(+), 27.9(+), 27.5(+), 25.8(–), 23.8(+), 22.7(+), 22.1(+), 18.0, 14.1(–), -4.4 , -4.9 (–); ν_{max} : 2924, 2853, 1738, 1464 cm^{-1} .

3.1.64. 5-(7-[(1*S*,2*R*)-2-((17*R*,18*R*)-17-Methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfonyl)-1-phenyl-1*H*-tetrazole (59). A solution of ammonium heptamolybdate(VI) tetrahydrate (0.36 g, 0.29 mmol) in ice cold H_2O_2 35% (w/w, 5 mL) was added dropwise to a stirred solution of 5-{7-[(1*S*,2*R*)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfonyl}-1-phenyl-1*H*-tetrazole (**55**) (0.50 g, 0.58 mmol) in THF (15 mL) and IMS (15 mL) at 5°C and stirred at room temperature for 1 h, then three more identical solutions of ammonium heptamolybdate(VI) tetrahydrate in ice cold H_2O_2 (35% w/w) were added over the next hour. The reaction mixture was stirred for 16 h at room temperature and then diluted with water (100 mL) and dichloromethane (50 mL). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×25 mL). The combined organic layers were washed with brine (50 mL), dried and evaporated to give a residue, which was purified by chromatography on silica eluting with petrol/diethyl ether (5:1) to give 5-(7-[(1*S*,2*R*)-2-((17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfonyl)-1-phenyl-1*H*-tetrazole (**59**) (0.48 g, 93%) [found $[\text{M}+\text{Na}^+]$: 919.7435; $\text{C}_{55}\text{H}_{100}\text{N}_4\text{NaO}_3\text{S}$ requires: 919.7408] $\{[\alpha]_{\text{D}}^{25} +4.40$ (c 1.0, CHCl_3)}, which showed δ_{H} (500 MHz, CDCl_3): 7.72–7.69 (2H, m), 7.64–7.59 (3H, m), 3.74 (2H, distorted t, J 7.9 Hz), 3.35 (3H, s), 2.97–2.94 (1H, m), 1.96 (2H, pent, J 7.6 Hz), 1.66–1.61 (1H, m), 1.53–1.48 (2H, m), 1.45–1.24 (70H, m), 1.18–1.06 (4H, m), 0.89 (3H, t, J 7.0 Hz), 0.86 (3H, d, J 7.0 Hz), 0.69–0.64 (2H, m), 0.58 (1H, dt, J 3.8, 7.9 Hz), -0.32 (1H, q, J 5.1 Hz); δ_{C} (125 MHz, CDCl_3): 153.5, 133.1, 131.4(–), 129.7(–), 125.1(–), 85.5(–), 57.7(–), 56.1(+), 35.4(–), 31.9(+), 30.5(+), 30.2(+), 30.0(+), 29.9(+), 29.8(+), 29.7(+), 29.4(+), 29.2(+), 29.0(+), 28.7(+), 28.6(+), 28.2(+), 27.6(+), 26.2(+), 25.1(+), 22.7(+), 22.0(+), 15.8(–), 15.7(–), 14.9(–), 14.1(–), 10.9(+); ν_{max} : 2908, 1596, 1499, 1464, 1343, 1153, 1099, 760 cm^{-1} .

3.1.65. (R)-2-[(R)-1-Acetoxy-18-[(1S,2R)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (60). Lithium hexamethyldisilazide (0.41 mL, 0.427 mmol, 1.06 M) was added dropwise to a stirred solution of ((1R,2R)-1-acetoxy-11-oxoundecyl)hexacosanoic acid methyl ester (**57**) (0.174 g, 0.274 mmol) and 5-[7-[(1S,2R)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptylsulfonyl]-1-phenyl-1H-tetrazole (**59**) (0.30 g, 0.33 mmol) in dry THF (10 mL) under nitrogen at -10°C . The mixture was allowed to reach room temperature and stirred for 1 h. When TLC showed no starting material, it was quenched with a satd aq ammonium chloride (5 mL) and diethyl ether (10 mL). The organic layer was separated and aqueous layer was re-extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine (20 mL), dried and evaporated to give a white solid, which was purified by chromatography on silica eluting with petrol/ether (10:1) to give (R)-2-[(E/Z)-(R)-1-acetoxy-18-[(1S,2R)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadec-11-enyl]-hexacosanoic acid methyl ester in ratio 2.3:1 (0.22 g, 60%). Hydrogenation with dipotassium azodicarboxylate and purification as before gave (R)-2-[(R)-1-acetoxy-18-[(1S,2R)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester as a semi solid (**60**) (194 mg, 90%) [found $[M+Na^+]$: 1332.3147; $C_{88}H_{172}NaO_5$ requires: 1332.3097] $\{[\alpha]_D^{25} +7.69$ (c 1.04, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 5.09 (1H, br td, J 3.8, 7.9 Hz), 3.68 (3H, s), 3.34 (3H, s), 2.98–2.95 (1H, m), 2.62 (1H, ddd, J 4.4, 7.0, 10.8 Hz), 2.04 (3H, s), 1.68–1.58 (4H, m), 1.56–1.48 (1H, m), 1.46–1.20 (138H, m), 1.19–1.05 (4H, m), 0.89 (6H, t, J 6.6 Hz), 0.85 (3H, d, J 6.9 Hz), 0.69–0.63 (2H, m), 0.57 (1H, dt, J 4.1, 7.9 Hz), -0.32 (1H, q, J 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 173.7, 170.3, 85.5(–), 74.1(–), 57.7(–), 51.5(–), 49.6(–), 35.4(–), 32.4(+), 31.9(+), 31.7(+), 30.5(+), 30.3(–), 30.2(+), 30.0(+), 29.9(+), 29.7(+), 29.65(+), 29.6(+), 29.4(+), 29.36(+), 28.7(+), 28.1(+), 27.6(+), 27.5(+), 26.2(+), 25(+), 22.7(+), 22.6(+), 21.0(–), 15.8(–), 14.9(–), 14.1(–), 10.9(+); ν_{max} : 2920, 1743, 1469, 1375, 1237, 1162, 719 cm^{-1}).

3.1.66. (R)-2-[(R)-1-(tert-Butyldimethylsilyloxy)-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester. Lithium hexamethyldisilazide (0.787 mL, 0.835 mmol, 1.06 M) was added dropwise to a stirred solution of (R)-2-[(R)-1-(tert-butyldimethylsilyloxy)-11-oxoundecyl]hexacosanoic acid methyl ester (**68**) (0.35 g, 0.49 mmol) and 5-[7-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptane-1-sulfonyl]-1-phenyl-1H-tetrazole (**56**) (0.575 g, 0.64 mmol) in dry THF (20 mL) under nitrogen at -12°C . The reaction was exothermic and the temperature rose to -5°C resulting in a dark orange solution. The mixture was allowed to reach room temperature and stirred for 2 h, when TLC showed that no starting material was left, cooled to 0°C and quenched with satd aq ammonium chloride (5 mL). The product was extracted with petrol/ether (2×50 mL), dried and evaporated to give a thick oil, which was purified by chromatography on silica eluting with petrol/ether (20:1) to give (E/Z)-(R)-2-[(R)-1-(tert-butyldimethylsilyloxy)-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatria-

contyl)cyclopropyl]octadec-11-enyl]hexacosanoic acid methyl ester in ratio (1.7:1) (0.52 g, 77%) as a thick colourless oil. Hydrogenation with dipotassium azodicarboxylate as before and chromatography on silica eluting with petrol/ether (20:1) gave (R)-2-[(R)-1-(tert-butyldimethylsilyloxy)-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester as a colourless viscous oil (0.405, 81%) [found $[M+Na^+]$: 1404.3887; $C_{92}H_{184}O_4SiNa$ requires: 1404.3856; found: C, 79.634; H, 13.435; $C_{92}H_{184}O_4Si$ requires: C, 79.925; H, 13.413] $\{[\alpha]_D^{25} +1.18$ (c 0.93, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 3.92–3.89 (1H, m), 3.66 (3H, s), 3.34 (3H, s), 2.98–2.95 (1H, m), 2.53 (1H, ddd, J 3.8, 7.0, 10.7 Hz), 1.66–1.10 (147H, m), 0.94–0.84 (18H, $3 \times CH_3$, $SiC(CH_3)_3$, $CHCH_3$), 0.69–0.64 (2H, m), 0.57 (1H, dt, J 3.8, 7.6 Hz), 0.053 (3H, s), 0.03 (3H, s), -0.32 (1H, br q, J 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 175.1, 85.5(–), 73.2(–), 57.7(–), 51.6(–), 51.2(–), 35.4(–), 33.7(+), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.0(+), 29.9(+), 29.8(+), 29.7(+), 29.65(+), 29.6(+), 29.4(+), 29.35(+), 28.7(+), 27.8(+), 27.6(+), 27.5(+), 26.2(+), 25.8(–), 23.7(+), 22.7(+), 18.0, 15.8(–), 14.9(–), 14.1(–), 10.9(+), -4.4 (–), -4.9 (–); ν_{max} : 2922, 2852, 1740, 1465, 1099 cm^{-1}).

3.1.67. (R)-2-[(R)-1-(tert-Butyldimethylsilyloxy)-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester. Lithium hexamethyldisilazide (1.24 mL, 1.32 mmol, 1.06 M) was added dropwise to a stirred solution of (R)-2-[(R)-1-(tert-butyldimethylsilyloxy)-11-oxoundecyl]hexacosanoic acid methyl ester (**68**) (0.35 g, 0.49 mmol) and 5-[7-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]heptane-1-sulfonyl]-1-phenyl-1H-tetrazole (**69**) (0.911 g, 1.01 mmol) in dry THF (25 mL) under nitrogen at -12°C . The mixture was allowed to reach room temperature and stirred for 2 h, when TLC showed that no starting material was left. It was quenched at 0°C with satd aq ammonium chloride (5 mL). Worked up and purified as above to give (E/Z)-(R)-2-[(R)-1-(tert-butyldimethylsilyloxy)-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadec-11-enyl]hexacosanoic acid methyl ester (0.94 g, 80%) as a thick colourless oil. Hydrogenation with dipotassium azodicarboxylate and purification as before gave (R)-2-[(R)-1-(tert-butyldimethylsilyloxy)-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester as a colourless viscous oil (0.68 g, 85%) $\{[\alpha]_D^{25} -4.4$ (c 1.62, $CHCl_3$) $\}$, which showed δ_H (500 MHz, $CDCl_3$): 3.91 (1H, br dt, J 5.1, 7 Hz), 3.66 (3H, s), 3.34 (3H, s), 2.96 (1H, br pent, J 4.1 Hz), 2.53 (1H, ddd, J 3.8, 7.3, 11.0 Hz), 1.7–1.05 (147H, m), 0.94–0.831 (18H, $2 \times CH_3$, $SiC(CH_3)_3$, $CHCH_3$), 0.67–0.64 (2H, m), 0.57 (1H, br dt, J 4.1, 7.9 Hz), 0.052 (3H, s), 0.03 (3H, s), -0.32 (1H, br q, J 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 175.1, 85.4(–), 73.2(–), 57.7(–), 51.6(–), 51.2(–), 35.3(–), 33.7(+), 32.4(+), 31.9(+), 30.5(+), 30.3(–), 30.2(+), 30.0(+), 29.9(+), 29.8(+), 29.7(+), 29.66(+), 29.6(+), 29.58(+), 29.56(+), 29.4(+), 29.36(+), 28.7(+), 27.8(+), 27.6(+), 27.5(+), 26.2(+), 25.8(–), 23.7(+), 22.7(+), 18.0, 15.8(–), 14.9(–), 14.1(–), 10.9(+), -4.4 (–), -4.9 (–); ν_{max} : 2922, 2852, 1740, 1465, 1099 cm^{-1}).

3.1.68. (R)-2-((R)-1-Hydroxy-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (72). A dry polyethylene vial equipped with a rubber septum was charged with (R)-2-((R)-1-(*tert*-butyldimethylsilyloxy)-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (0.35 g, 0.253 mmol) and pyridine (0.4 mL) in dry tetrahydrofuran (15 mL) and stirred at room temperature under argon. To it was added hydrogen fluoride–pyridine complex (1.2 mL). The mixture was stirred at 43 °C for 17 h; when TLC showed that no starting material was left, the mixture was neutralised by pouring slowly into satd aq sodium bicarbonate until no more CO₂ was liberated. The product was extracted with petrol/ether (5:2) (3×25 mL), dried, evaporated to give a white solid and purified by chromatography eluting with petrol/ether (5:1) to give (R)-2-((R)-1-hydroxy-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester as a white solid (**72**) (0.27 g, 84%), mp 63–64 °C [found [M+Na⁺]: 1290.3046; C₈₆H₁₇₀O₄Na requires: 1290.2991; found: C, 81.208; H, 13.614; C₈₆H₁₇₀O₄ requires: C, 81.444; H, 13.509] {[α]_D²⁵ +6.0 (c 1.15, CHCl₃)}, which showed δ_H (500 MHz, CDCl₃): 3.72 (3H, s), 3.69–3.64 (1H, m), 3.34 (3H, s), 2.97–2.94 (1H, m), 2.44 (1H, tt, *J* 5.4, 9.5 Hz), 1.74–1.06 (148H, m), 0.91–0.84 (9H, including t, *J* 6.6 Hz for 2×CH₃, and d, *J* 6.6 Hz for CHCH₃), 0.68–0.63 (2H, m), 0.57 (1H, dt, *J* 4.1, 8.2 Hz), –0.32 (1H, br q, *J* 5.1 Hz); δ_C (125 MHz, CDCl₃): 176.2, 85.5(–), 72.3(–), 57.7(–), 51.5(–), 50.9(–), 35.7(+), 35.4(–), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.0(+), 29.9(+), 29.7(+), 29.63(+), 29.6(+), 29.58(+), 29.56(+), 29.55(+), 29.5(+), 29.4(+), 29.36(+), 28.7(+), 27.6(+), 27.4(+), 26.2(+), 25.7(+), 22.7(+), 15.8(–), 14.9(–), 14.1(–), 10.9(+); ν_{max}: 3355, 2923, 2852, 1712, 1462 cm^{–1}.

3.1.69. (R)-2-((R)-1-Hydroxy-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (70). A dry polyethylene vial equipped with a rubber septum was charged with (R)-2-((R)-1-(*tert*-butyldimethylsilyloxy)-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (0.6 g, 0.434 mmol) and pyridine (0.5 mL) in dry tetrahydrofuran (15 mL) and stirred at room temperature under argon. To it was added hydrogen fluoride–pyridine complex (1.8 mL). The mixture was stirred at 43 °C for 17 h, when TLC showed that no starting material was left, then worked up and purified as above to give (R)-2-((R)-1-hydroxy-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (**70**) as a white solid (0.46 g, 83%), mp 59–61 °C [found [M+Na⁺]: 1290.2974; C₈₆H₁₇₀O₄Na requires: 1290.2991] [found: C, 81.699; H, 13.518; C₈₆H₁₇₀O₄ requires: C, 81.444; H, 13.509] {[α]_D²⁵ –1.04 (c 1.15, CHCl₃)}, which showed δ_H (500 MHz, CDCl₃): 3.72 (3H, s), 3.69–3.64 (1H, m), 3.34 (3H, s), 2.97–2.94 (1H, br pent, *J* 4.4 Hz), 2.46–2.41 (2H, m, CHCO, OH, after shaking with D₂O, integration showed only one proton), 1.74–1.12 (147H, m), 0.90–0.83 (9H, including t, *J* 7.0 Hz, for 2×CH₃, d, *J* 7.0 Hz, for CHCH₃), 0.68–0.64 (2H, m), 0.565 (1H, dt, *J* 4.1, 8.2 Hz), –0.326 (1H, br q, *J* 5.1 Hz); δ_C (125 MHz, CDCl₃): 176.2, 85.4(–), 72.3(–), 57.7(–), 51.5(–), 50.9(–), 35.7(+),

35.3(–), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.0(+), 29.9(+), 29.74(+), 29.7(+), 29.64(+), 29.6(+), 29.58(+), 29.56(+), 29.55(+), 29.5(+), 29.4(+), 29.36(+), 28.7(+), 27.57(+), 27.4(+), 26.2(+), 25.7(+), 22.7(+), 15.8(–), 14.9(–), 14.1(–), 10.9(+); ν_{max}: 3355, 2923, 2852, 1712, 1462 cm^{–1}.

3.1.70. (R)-2-((R)-1-Hydroxy-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid (71). Lithium hydroxide monohydrate (75.64 mg, 1.845 mmol) was added to a stirred solution of (R)-2-((R)-1-hydroxy-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (**70**) (156 mg, 0.123 mmol) in tetrahydrofuran (15 mL), methanol (2 mL) and water (1.2 mL) at room temperature. The mixture was stirred at 43 °C for 24 h, when TLC showed that a very small amount of starting material was left. It was cooled to room temperature, quenched with satd ammonium chloride (5 mL), diluted with petrol/ether (1:1) (30 mL) and then acidified with 5% HCl. The organic layer was separated and the aqueous layer was re-extracted with petrol/ethyl acetate (1:1) (2×50 mL). The combined organic layers were dried, evaporated and purified by chromatography on silica eluting with petrol/ethyl acetate (7:2) to give (R)-2-((R)-1-hydroxy-18-[(1R,2S)-2-((17S,18S)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid (**71**) as a white solid (102 mg, 66%), mp 65–67 °C [found [M+Na⁺]: 1276.2771; C₈₅H₁₆₈O₄Na requires: 1276.2835] [found: C, 81.0; H, 13.1; C₈₅H₁₆₈O₄ requires: C, 81.40; H, 13.50] {[α]_D²⁵ –1.07 (c 1.4, CHCl₃)}, which showed δ_H (500 MHz, CDCl₃): 3.73–3.70 (1H, m, CHOMe), 3.35 (3H, s, OMe), 2.99–2.96 (1H, m, CHOH), 2.49–2.45 (1H, m, CHCO), 1.79–1.71 (1H, m, saturated alkane), 1.67–1.61 (2H, m, saturated alkane), 1.55–1.08 (146H, m, saturated alkane), 0.91–0.85 (9H, including t, *J* 6.6 Hz, for 2×CH₃, a doublet *J* 6.6 Hz, for CHCH₃), 0.69–0.64 (2H, m, 2×–CH-cyclopropane), 0.57 (1H, dt, *J* 3.7, 7.9 Hz, one HCH, of the cyclopropane), –0.32 (1H, br q, *J* 4.7 Hz, one HCH-cyclopropane); δ_C (125 MHz, CDCl₃): 179.2, 85.6(–), 72.1(–), 57.7(–), 50.8(–), 35.6(+), 35.3(–), 32.4(+), 31.9(+), 30.5(+), 30.2(+), 30.0(+), 29.9(+), 29.7(+, v br), 29.6(+), 29.59(+), 29.5(+), 29.4(+), 29.36(+), 28.7(+), 27.6(+), 27.3(+), 26.2(+), 25.7(+), 22.7(+), 15.8(–), 14.9(–), 14.1(–), 10.9(+); ν_{max}: 3516, 2917, 2850, 1718, 1462 cm^{–1}.

3.1.71. (R)-2-((R)-1-Hydroxy-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid (73). Lithium hydroxide monohydrate (48.6 mg, 1.185 mmol) was added to a stirred solution of (R)-2-((R)-1-hydroxy-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid methyl ester (**72**) (100 mg, 0.079 mmol) in tetrahydrofuran (10 mL), methanol (1.5 mL) and water (0.8 mL) at room temperature. The mixture was stirred at 43 °C for 24 h. When TLC showed no starting material, the reaction was worked up and purified as above to give (R)-2-((R)-1-hydroxy-18-[(1R,2S)-2-((17R,18R)-17-methoxy-18-methylhexatriacontyl)cyclopropyl]octadecyl]hexacosanoic acid (**73**) as a yellowish solid (62 mg, 63%) [found [M–H⁺]: 1252.2804; C₈₅H₁₆₇O₄ requires: 1252.2859] {[α]_D²⁵ +6.95 (c 1.05, CHCl₃)}, which showed δ_H (500 MHz, CDCl₃): 3.73–3.70 (1H, m, CHOMe), 3.35 (3H, s, OMe), 2.99–2.95 (1H,

m, CHOH), 2.48–2.44 (1H, m, CHCO), 1.79–1.71 (1H, m, saturated alkane), 1.67–1.61 (2H, m, saturated alkane), 1.55–1.08 (146H, m, saturated alkane), 0.903–0.83 (9H, including t, J 7.0 Hz, for $2\times\text{CH}_3$, d, J 7.0 Hz, for CHCH_3), 0.68–0.63 (2H, m, $2\times\text{-CH-cyclopropane}$), 0.56 (1H, br dt, J 4.1, 8.2 Hz, one HCH of the cyclopropane), -0.326 (1H, br q, J 5.1 Hz, one HCH-cyclopropane); δ_{C} (125 MHz, CDCl_3): 178.8, 85.6(–), 72.1(–), 57.7(–), 50.7(–), 35.6(+), 35.3(–), 32.4(+), 31.9(+), 30.5(+), 30.3(+), 30.2(+), 30.0(+), 29.9(+), 29.7(+), 29.66(+), 29.6(+), 29.58(+), 29.5(+), 29.4(+), 29.36(+), 28.7(+), 27.6(+), 27.3(+), 26.1(+), 25.7(+), 22.7(+), 15.8(–), 14.9(–), 14.1(–), 10.9(+); ν_{max} : 3516, 2917, 2850, 1718, 1462 cm^{-1} .

3.1.72. Hydrolysis of (*R*)-2-[(*R*)-1-acetoxy-18-[(1*R*,2*S*)-2-[(17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl]-cyclopropyl]octadecyl]hexacosanoic acid methyl ester with lithium hydroxide. Lithium hydroxide monohydrate (31.2 mg, 0.76 mmol) was added to a stirred solution of (*R*)-2-[(*R*)-1-acetoxy-18-[(1*R*,2*S*)-2-[(17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl]cyclopropyl]octadecyl]hexacosanoic acid methyl ester (**58**) (50 mg, 0.038 mmol) in tetrahydrofuran (8 mL), methanol (1 mL) and water (0.5 mL) at room temperature. The mixture was stirred at 43 °C for 24 h. When TLC showed that no starting material was left, the reaction was cooled to room temperature, diluted with petrol/ether (1:1) (30 mL) and ammonium chloride (5 mL) then acidified with 5% HCl. The organic layer was separated and the aqueous layer was extracted with petrol/ether (2×20 mL). The combined organic layers were dried, evaporated to give a white solid, which was purified by chromatography on silica eluting with petrol/ethyl acetate (5:2) to give (*R*)-2-[(*R*)-1-hydroxy-18-[(1*R*,2*S*)-2-[(17*R*,18*R*)-17-methoxy-18-methylhexatriacontyl]cyclopropyl]octadecyl]-hexacosanoic acid (**73**) (32 mg, 67%), which showed an identical spectrum to that above.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.01.007.

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