Tetrahedron 70 (2014) 7322–7335

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthetic epoxy-mycolic acids

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ARTICLE INFO

Article history:
Received 30 April 2014
Received in revised form 12 June 2014
Accepted 20 June 2014
Available online 2 July 2014

Keywords:
Mycolic acid
Environmental
Mycobacteria
Epoxy

ABSTRACT

We report the synthesis of single enantiomers of epoxy-mycolic acids containing an α-methyl-*trans*-alkene or a *cis*-cyclopropane with structures that match those of major isomers of such molecules present in complex mixtures in Mycobacteria such as *Mycobacterium fortuitum* or *Mycobacterium smegmatis*

1. Introduction

Mycolic acids (MAs), **1** (Fig. 1), are major constituents of the cell envelope of *Mycobacterium tuberculosis* and other mycobacteria, some of which are pathogenic to animals and humans.[1–3] Their structure and biosynthesis has been reviewed,[4] and a number of structural and stereochemical relationships examined.[5] Their presence is thought to be linked to the resistance of these organisms to most current antibiotics and other chemotherapeutic agents.[6]

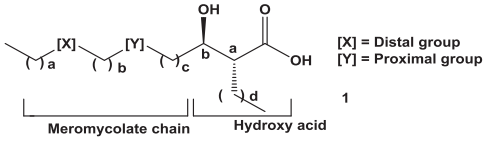
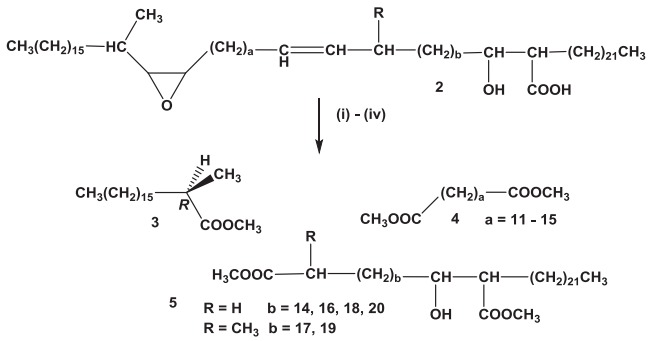


Fig. 1. The typical structure of a mycolic acid.

The two stereocentres in the α and β-positions relative to the carboxylic group have both been found to be in the *R*-configuration for all the mycolic acids examined, irrespective of the other functional groups.[7,8] In each case 'a–d' represent long alkyl chains, and generally each *Mycobacterium* contains a mixture of several homologues. In the common classes of MA, the proximal group is often a cyclopropane or an alkene and the distal group is a cyclopropane (α-MA), an α-methoxy-β-methyl fragment (methoxy-MA) or an α-keto-β-methyl fragment (keto-MA).[2,3] In 1981, Daffé et al. reported the identification of a new kind of mycolic acid in *Mycobacterium fortuitum* containing an α-methyl epoxy-group at the distal position and an alkene at the proximal position (**2**, R=H) (Scheme 1).[9] Minnikin et al. later described the presence of similar molecules in *M. fortuitum*, *Mycobacterium farcinogenes*, *Mycobacterium senegalense*, '*Mycobacterium peregrinum*', and *Mycobacterium smegmatis*;[10–12] in these cases the major isomers had a *cis*-alkene at the proximal position, but there was a minor component (ca. 30% by NMR spectroscopy) (**2**, R=Me) containing a proximal α-methyl-*trans*-alkene; the major isomer of the latter contained 78 carbons; the epoxy-MA had carbon skeletons similar to those in methoxy-, keto- or α-MA described earlier.[10]



Scheme 1. (i) Acetolysis; (ii) saponification; (iii) oxidative cleavage; (iv) methylation.

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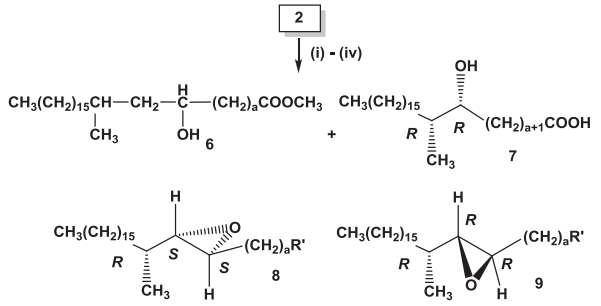
http://dx.doi.org/10.1016/j.tet.2014.06.089
0040-4020/

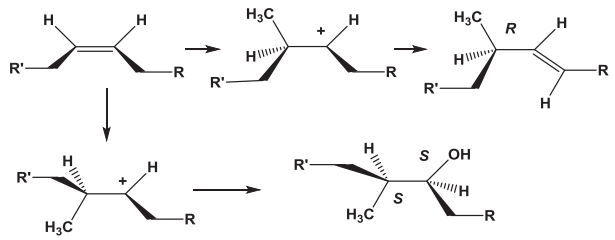
Epoxy-MAs are also present in *Mycobacterium chitae*,[13,14] '*Mycobacterium giae*',[13] *M. peregrinum*,[11–13] *Mycobacterium porcinum* and *M. senegalense*,[15] and in a mutant strain of *M. tuberculosis*.[16] In the final case, these included epoxy-MA with a *cis*-cyclopropane at the proximal position. Epoxy-mycolic acids have also been detected directly by MALDI-TOF mass spectrometry; the major isomers containing a *trans*-alkene at the proximal position are reported to be C_{78} and C_{80} molecules.[16–18] Studies using *M. smegmatis* have identified the function of the protein *MSMEG0913* in adding the methyl branch adjacent to both an alkene and a cyclopropane at the proximal position of epoxy-mycolates to produce the *trans*-homologues,[18] and examined other aspects of the biochemistry of such species.[19–22] The relative and absolute stereochemistry of epoxy-mycolates containing a proximal *cis*- or α-methyl-*trans*-alkene has been probed by two methods (Scheme 1).[23] Firstly, opening of the epoxide **2** by acetolysis, then saponification and oxidative cleavage of both the derived 1,2-diol and the alkene leads to three products, including (*R*)-ester **3**.

Secondly, reductive ring-opening of the epoxide **2** followed by oxidative cleavage of the proximal alkene, saponification and methylation led to the two acids **6** and **7** (Scheme 2). The latter was shown to have *R*,*R*-stereochemistry by comparison to a model compound. On this basis the authors assigned all the stereocentres in the epoxy-mycolic acid as *R*.[23] However, it seems clear in fact that the result actually suggests the epoxy fragment is *R*,*S*,*S* as in **8** rather than *R*,*R*,*R* as in **9**, the priorities in the epoxide being different from those in the ring-opened alcohol.



Scheme 2. (i) Reduction; (ii) oxidative cleavage; (iii) saponification; (iv) methylation.

What is arguably most interesting is that the methyl group adjacent to the epoxide is in the *R*-configuration, whereas that adjacent to the hydroxyl, methoxy or keto-groups at the distal position of the corresponding mycolic acids is of S-configuration. It is attractive to propose that the various types of mycolic acid are formed through a formal intermediate carbocation, formed by methylation of a *cis*-alkene by SAM (Scheme 3). Methylation from the *Re* or *Si* face of the alkene at the alkylated carbon could then lead to a divergence in stereochemistry.

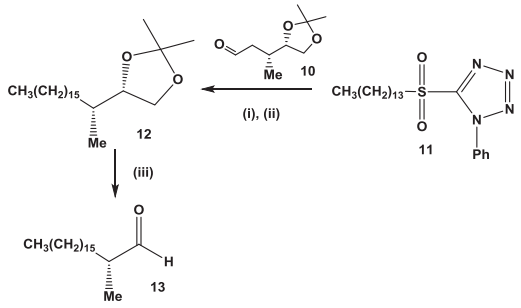


Scheme 3. Possible formal mechanism for production of *S*- and *R*-methyl branches by methylation of a *cis*-alkene by SAM.

We have reported the synthesis of an α-mycolic acid,[24,25] of methoxymycolic acids with either absolute stereochemistry at the *cis*-cyclopropane or α-methyl-β-methoxy fragment,[26] and of keto mycolic acids.[27,28] We have also reported the synthesis of methoxy and keto mycolic acids containing an α-methyl-*trans*-cyclopropane unit,[29,30] of *cis*-alkene mycolic acids,[31] and of hydroxy- and keto mycolic acids containing an (*R*)-α-methyl-*trans*-alkene unit.[32] We now report in full the synthesis of two stereoisomeric epoxy-mycolic acids containing an (*R*)-α-methyl-*trans*-alkene at the proximal position; these have the chain lengths reported for one mycolic acid in *M. fortuitum*,[4,5] and the total carbon number is consistent with those observed for one component of a mixture from *M. smegmatis* by MALDI mass spectrometry.[17,18] This has been reported briefly earlier.[33] We also report the synthesis of an epoxy-mycolic acid containing a *cis*-cyclopropane.

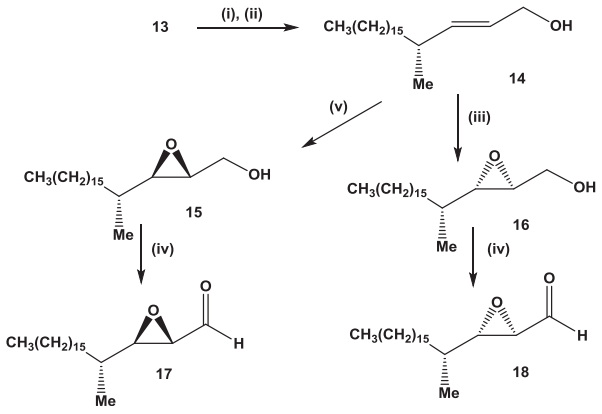
2. Results and discussion

The aldehyde **13** was first prepared from the known aldehyde **10**,[28,34,35] with sulfone **11** (see Supplementary data) and base in a modified Julia-Kocienski reaction, followed by hydrogenation to give **12**. Deprotection and oxidative cleavage of the acetal **12** led to **13** (Scheme 4).



Scheme 4. (i) **10,** $LiN(SiMe_3)_2$ (LiBSA), THF, −10 °C (67%); (ii) H_2, Pd/C, ethanol, (92%); (iii) periodic acid, dry ether (77%).

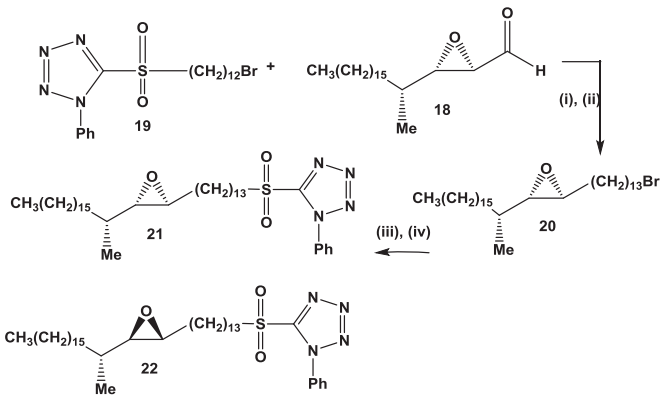
A Wittig reaction and then reduction with DIBAL led to the *trans*-alcohol **14** (Scheme 5). Asymmetric epoxidation using Sharpless conditions provided the two diastereoisomers **15** and **16**.[36,37] The two epoxides showed $[\alpha]_D^{22}$ of +18.1 and −21.2, respectively. The literature value for (2*R*,3*R*)-dodecyloxiranyl-methanol is −25.5.[38]



Scheme 5. (i) $Ph_3P{=}CHCOOMe$, toluene (65%); (ii) DIBAL, CH_2Cl_2 (95%); (iii) L-(+)-diethyl tartrate, $Ti(Oi\text{-}Pr)_4$, *t*-BuOOH, CH_2Cl_2, −20 °C (75%); (iv) PCC, CH_2Cl_2 (59%, **18**), (60%, **17**); (v) D-(−)-diethyl tartrate, $Ti(Oi\text{-}Pr)_4$, *t*-BuOOH, CH_2Cl_2, −20 °C (67%).

Oxidation of each alcohol led to the corresponding aldehyde. The aldehyde **18** was chain extended by reaction with the sulfone **19** (see Supplementary data) and base, followed by saturation of the derived alkene using di-imide. The derived bromide **20**, $[\alpha]_D^{22}$ −13.1 (*c* 1.2, $CHCl_3$) ($[M]_D$ −76) {molecular rotation, $[M]_D$ = (molecular weight×specific rotation)/100}, was then converted into the corresponding sulfone **21**. In the same manner, diastereoisomer **17** was converted into **22** (Scheme 6). The molecular rotations of the two

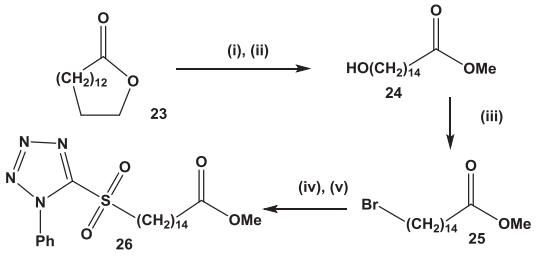
diastereomeric sulfones **21** and **22** were −58 and +43, respectively. This may provide an approximate value for the contribution of this chiral unit to the molecular rotations of mycolic acids containing these fragments.



Scheme 6. (i) LiBSA, THF, −10 °C (71%); (ii) $KO_2CN{=}NCO_2K$, AcOH, THF, MeOH (93%); (iii) 1-phenyl-1*H*-tetrazole-5-thiol, acetone, K_2CO_3 (82%); (iv) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (industrial methylated spirit), THF (67%).

The NMR spectra of the isomers **21** and **22** (see Supplementary data), and of each pair of precursors were very similar. However, in each case, those of the series leading to **21** showed a double triplet for the epoxide hydrogen adjacent to the methylene group at δ 2.72 (J 2.2, 5.7 Hz), with a coupling constant of around 2.2 Hz to the second epoxide hydrogen, a double doublet at δ 2.41 (J 2.2, 7.0 Hz); apparently the coupling constants between the former hydrogen and the two diastereotopic methylene hydrogens are equal. The methyl group adjacent to the epoxide appeared as a doublet at δ 1.0. In the ^{13}C NMR spectrum, the two epoxide carbons appeared at δ 63.8 and 58.8. In the series leading to **22**, the corresponding hydrogen signals appeared at δ 2.66 and 2.45, with approximately similar coupling constants, while the methyl signal appeared at δ 0.91–0.92. In this case the epoxide carbons appeared at ca. δ 63.7 and 57.4. The ^1H NMR spectra for **21** and **22** each showed minor impurities corresponding to the other diastereoisomer, probably arising from a small amount of epimerization of the aldehyde **13**.

In order to obtain the α-methyl-*trans*-alkene unit the sulfone **26** was first prepared from lactone **23** (Scheme 7):[39]

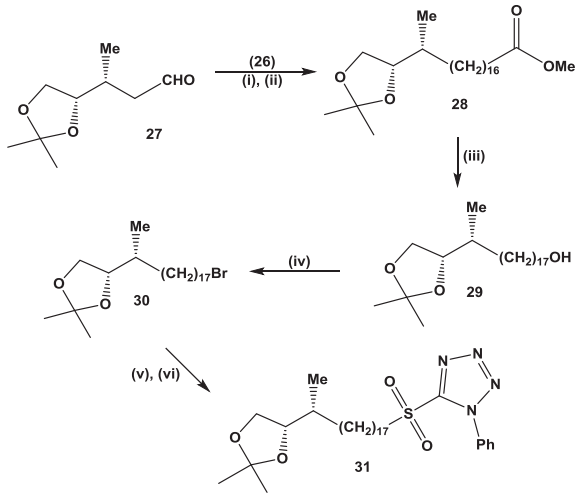


Scheme 7. (i) NaOMe, MeOH; (ii) H_2SO_4, MeOH, reflux (85% for two steps) (iii) Ph_3P, NBS, $NaHCO_3$, CH_2Cl_2 (88%) (iv) 1-phenyl-1*H*-tetrazole-5-thiol, K_2CO_3, acetone (90%); (v) $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, H_2O_2, THF/IMS (91%).

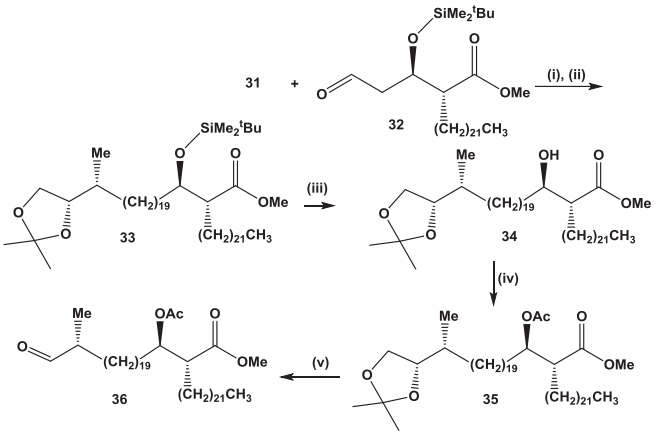
Chain extension of the aldehyde **27**, prepared as described earlier,[28,34,35] with the sulfone **26** and base, followed by saturation of the derived mixture of alkenes and then conversion into the sulfone **31** was achieved by standard methods (Scheme 8).

Reaction of the sulfone **31** with aldehyde **32**[28,31] and base, followed by saturation of the alkenes produced, led to the acetal **33**. This could be transformed into aldehyde **36** by changing the protecting group to acetate followed by oxidative cleavage (Scheme 9).

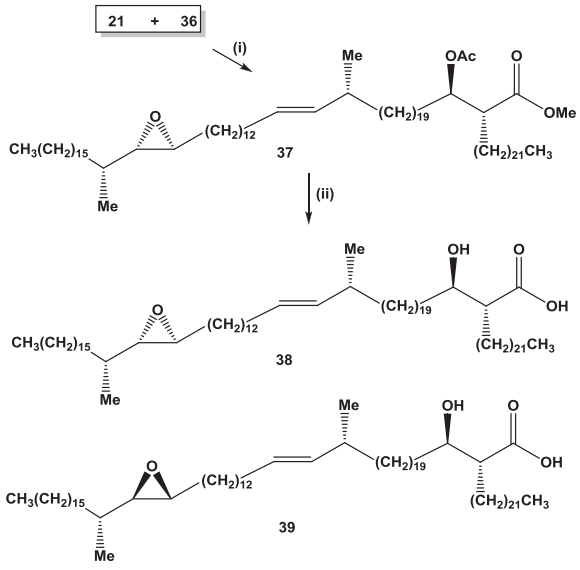
Finally, coupling of **36** and **21** in the presence of base led to the protected epoxy-mycolic acid **37**, using the method described earlier.[28] Compound **37** could be deprotected to **38** (Scheme 10). In



Scheme 8. (i) LiBSA, −10 °C (61%); (ii) H_2, Pd/C, IMS, THF (93%); (iii) $LiAlH_4$, THF (91%); (iv) NBS, Ph_3P, CH_2Cl_2 (96%); (v) 1-phenyl-1*H*-tetrazole-5-thiol, K_2CO_3, acetone (90%); (vi) $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, H_2O_2, THF/IMS (92%).



Scheme 9. (i) LiBSA, THF, −10 °C (89%); (ii) H_2, Pd/C, IMS, THF (95%); (iii) HF·pyridine, pyridine, THF (80%); (iv) Ac_2O, pyridine, toluene (98%); (v) HIO_4, Et_2O (64%).

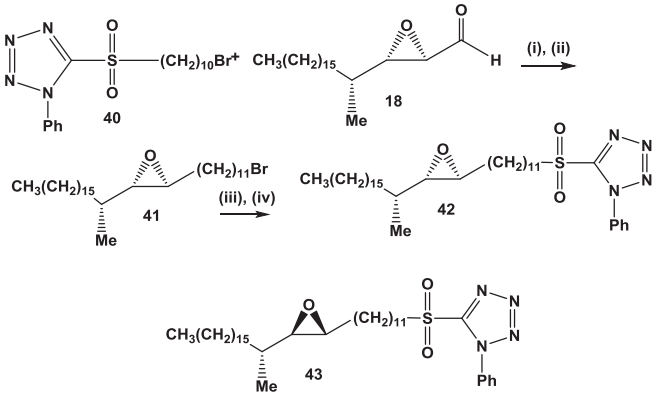


Scheme 10. (i) KBSA, 1,2-dimethoxyethane, −5 °C (26%); (ii) LiOH, THF, H_2O, MeOH, 45 °C (70%).

the same way **39** was obtained from **22**. Compound **38** showed a MALDI mass ion corresponding to one homologue of the natural mixture.[18] The specific rotation of compound **38** corresponded to a molecular rotation of −66, while that of **39** was +72. The proton NMR spectrum of **38** showed signals for the two epoxide hydrogens at δ 2.73 (1H, dt, *J* 2.2, 5.3 Hz) and 2.43 (1H, dd, *J* 2.2, 7.3 Hz) and two methyl doublets at δ 1.0 and 0.94. The *trans*-alkene hydrogens appeared as a characteristic double triplet at δ 5.33 and double doublet at 5.24, with a coupling of 15.2 Hz between them. The carbons of the epoxide appeared at δ 64.0 and 59.0 in the ^{13}C NMR spectrum. As in the case of the intermediates leading to **38** and **39**, while the two epoxide hydrogens and the methyl adjacent to the epoxide of **38** appeared at the positions described above, the corresponding proton signals for **39** appeared at δ 2.68, 2.47, and 0.92; the epoxide carbons appeared at δ 63.9 and 57.6. The proton spectra of these two compounds are reproduced in the Supplementary data. The signals for **38** visually correspond well (Supplementary data) with those reported by Laval et al. for a fraction of natural *trans*-alkene containing epoxy-MA.[18] Epoxymycolates present in *M. smegmatis* are reported to show a double doublet at δ 2.43 and a broad triplet at δ 2.72 and methyl signals at δ 1.02 and 0.92.[18] An earlier paper reports the chemical shifts as δ 2.39 and 2.70, with the signal for the methyl adjacent to the epoxide appearing at δ 0.98 and that adjacent to the alkene at δ 0.92; the epoxide carbons are reported to appear at δ 63.7 and 58.6.[10,40] The shape and position of the signal for the epoxide hydrogen adjacent to the chain methylene group for **38** is very similar to that shown for the corresponding proton in *Mycobacterium confluentis* and *M. smegmatis*.[41]

This method produces an epoxy-MA **38** with the same chain lengths as those reported for one natural example, and molecular rotations for fragments, which are consistent with those reported. Moreover, by simple variation, the method can be adjusted to provide a *trans*-alkene containing epoxy-MA of any necessary chain length and varying absolute stereochemistry.

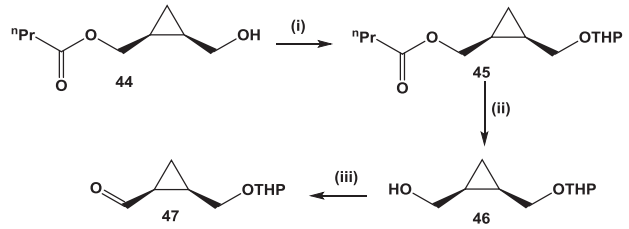
In the second part of this work, a *cis*-cyclopropane containing epoxy-mycolic acid,[16,17,40] was prepared. The epoxy-sulfones **42** and **43** were first prepared from aldehydes **18** and **17** using a similar method to that above (Scheme 11).



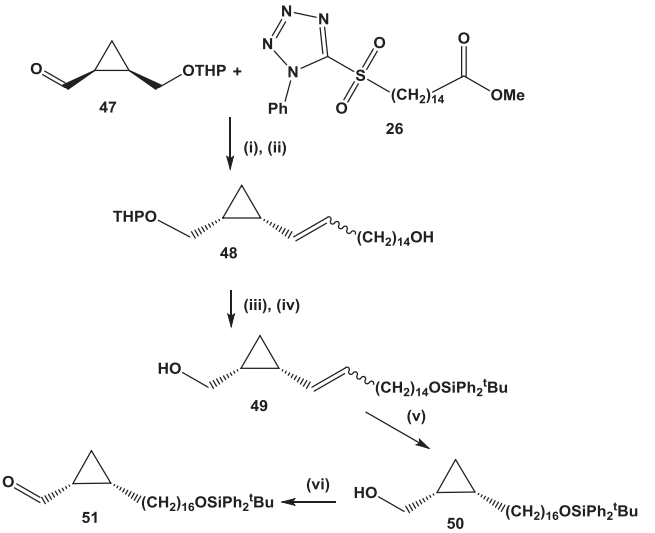
Scheme 11. (i) LiBSA, THF, −10 °C (63%); (ii) $KO_2CN{=}NCO_2K$, AcOH, THF, MeOH (96%); (iii) 1-phenyl-1*H*-tetrazole-5-thiol, acetone, K_2CO_3 (71%); (iv) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS, THF (84%).

The *cis*-cyclopropane was introduced using the aldehyde **47** prepared from the butyrate **44** (Scheme 12):[42]

Coupling of **47** with **26** and base, followed by hydrogenation of the derived alkene mixture and functional group modification provided the chain extended aldehyde **51** (Scheme 13):

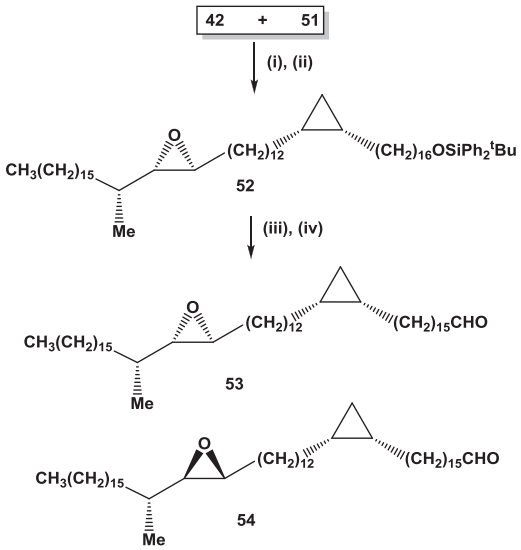


Scheme 12. (i) PPTS, CH_2Cl_2, 3,4-dihydro-2*H*-pyran (84%); (ii) $LiAlH_4$, THF (92%); (iii) PCC, CH_2Cl_2 (54%).



Scheme 13. (i) LiBSA, THF, −10 °C (89%); (ii) $LiAlH_4$, THF (80%); (iii) $^tBuPh_2SiCl$, Et_3N, CH_2Cl_2 (95%); (iv) PPTS, MeOH/THF 50 °C (82%); (v) $KO_2CN{=}NCO_2K$, AcOH, THF, MeOH (98%); (vi) PCC, CH_2Cl_2 (98%).

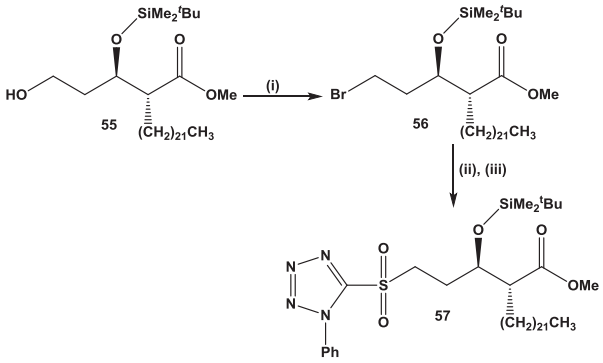
A second coupling of **42** and **51**, followed again by saturation of the alkene provided **52**, which was deprotected and oxidized to **53**. In the same way **43** was converted into **54** (Scheme 14).



Scheme 14. (i) LiBSA, THF, −10 °C (89%); (ii) $KO_2CN{=}NCO_2K$, AcOH, THF, MeOH (80%); (iii) TBAF, THF (91%); (iv) PCC, CH_2Cl_2 (76%).

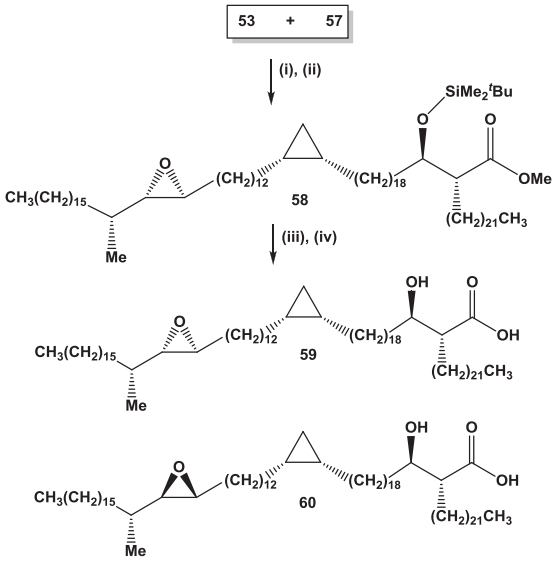
The molecular rotation of the aldehyde **53** was −81, compared to the diastereomer **54**, at +60. These values correspond reasonably well with those for the two epoxide fragments **21** and **22**, reflecting the modest contribution of the *cis*-cyclopropane to the molecular rotation.

In order to achieve the coupling to form the complete mycolic acid, the known alcohol **55**,[31] was first transformed into the sulfone **57** (Scheme 15):



Scheme 15. (i) NBS, PPh_3, CH_2Cl_2 (60%); (ii) 1-phenyl-1*H*-tetrazole-5-thiol, acetone, K_2CO_3 (95%); (iii) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS, THF (90%).

Coupling of aldehyde **53** to sulfone **57** provided the protected epoxy-mycolic acid **58**, which was deprotected to the free acid **59**. In the same way, compound **54** was converted into **60**. This corresponds to the formula of one of three isomers reported to be present in the epoxy-MA fraction of *M. smegmatis* (Scheme 16).[18]



Scheme 16. (i) LiBSA, THF, −2 °C (68%); (ii) $KO_2CN{=}NCO_2K$, AcOH, THF, MeOH (92%); (iii) HF·pyridine, pyridine, THF (56%); (iv) LiOH, THF, MeOH 45 °C (76%).

The proton NMR spectrum of **59** corresponded to that reported.[40] Thus the epoxide protons appeared at δ 2.73 (2.73 in the natural mixture) and 2.43 (2.42), the methyl adjacent to the epoxide at 1.00 (1.01), and the cyclopropane protons at 0.65–0.69 (0.65), 0.56 (0.57), −0.32 (−0.32).[40]

The molecular rotation of hydroxy acid **59** was −97, while that of the diastereoisomer **60** was +144. Those of the precursor methyl esters were −23 and +61, respectively. The molecular rotations of individual functional groups in natural mixtures of mycolic acids and in model compounds have been identified by Quemard et al.[43] In general $[M]_D$ in such systems where groups of chiral centres are separated by long carbon chains are approximately additive; the individual values for the *R*,*R*-centres of the 2-hydroxy acid (ester) fragment in mycolates is estimated as +40, the R–CH=CHCH$_3$– fragment as −25 (for 30% content). The figure for the α-methyl-epoxide fragments such as **21** and **22** may be estimated from the present results as −60 and +45 (see Supplementary data). In the case of the methyl ester of **59** and **60**, the contribution form the *cis*-cyclopropane is expected to be very small (as seen above), the chirality arising only from differences in the two substituents, both involving very long chains. Using a notional value of 0 for this, the M_D values for the two compounds can be estimated as −20 (−60+40) and +85 (+45+40) based on the sum of the epoxide and hydroxy acid contributions; the two methyl esters gave experimental values of −24 and +62. A more detailed analysis of the contributions of the synthetic fragments to the $[M]_D$ will be presented elsewhere.

3. Conclusion

Although first described relatively late in the understanding of mycolic acids in mycobacteria,[9] epoxy-mycolic acids have been identified in a large number of organisms. As with many individual mycolic acids, the specific chain lengths are often not fully identified; however, although the absolute stereochemistry of some groups present in MA even now remains uncertain that of epoxy-MA has been well defined at least from one organism.[23] This paper describes the synthesis of epoxy-MA of that stereochemistry, containing either a proximal α-methyl-*trans*-alkene or a *cis*-cyclopropane. Synthetic mycolic acids corresponding to the three major classes present in pathogenic mycobacteria such as *M. tuberculosis* have been shown to elicit strong and differential responses in assays to determine their effect on the immune system.[44,45] They also behave as antigens to antibodies in the serum of patients with active tuberculosis, albeit with modest sensitivity and specificity in standard ELISA assays.[46] Studies of the effects of epoxy-MA in a range of assays to determine their immune system effects are ongoing. In a preliminary study to determine whether they bind to antibodies in the serum of patients with active tuberculosis using a standard ELISA approach, there was no difference in the average response with 10 TB-positive and 40 TB-negative samples from samples taken in several countries where TB is indigenous when compound **39** was used as the antigen.[47] This is perhaps not unexpected, as these MA are not significant components of *M. tuberculosis*.

4. Experimental section

4.1. General

Chemicals used were obtained from commercial suppliers (Sigma, Aldrich, and Alfa Aeser) or prepared from them by the methods described. Solvents, which were required to be dry, e.g., ether, tetrahydrofuran were dried over sodium wire and benzophenone under nitrogen, while dichloromethane was dried over calcium hydride. Petroleum spirit (petrol) was of boiling point 40–60 °C. All reagents and solvents used were of reagent grade unless otherwise stated. Silica gel (Merck 7736) and silica gel plates used for column chromatography and thin layer chromatography were obtained from Aldrich; separated components were detected using variously UV light, I_2 and phosphomolybdic acid solution in IMS followed by charring. Anhydrous magnesium sulfate was used to dry organic solutions. Infra-red (IR) spectroscopy was carried out on a Perkin–Elmer 1600 FTIR spectrometer as liquid films or KBr disc (solid). Melting points were measured using a Gallenkamp melting point apparatus. NMR spectroscopy was carried out on Bruker Avance 400 or 500 spectrometers. $[\alpha]_D$ values were recorded in $CHCl_3$ on a POLAAR 2001 optical activity polarimeter. Mass spectra were recorded on a Bruker MALDI-TOF MS) to an accuracy of 2 d.p.; accurate mass values were obtained on a Bruker Microtof LC–MS.

In general, for those compounds synthesised in two stereochemistries, the experimental details are presented here for only one series; the details for the other series are provided in Supplementary data.

4.1.1. (S)-2,2-Dimethyl-4-((R)-1-methylheptadecyl)-[1,3]dioxolane. Lithium bis(trimethylsilyl)amide (50 mL, 52 mmol, 1.06 M) was added dropwise with stirring to (*R*)-3-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-butyraldehyde **10**[28,34,35] (5.42 g, 31.5 mmol) and 5-(tetradecane-1-sulfonyl)-1-phenyl-1*H*-tetrazole **11** (see Supplementary data) (16.6 g, 40 mmol) in dry tetrahydrofuran (250 mL) under nitrogen at −2 °C. The mixture was allowed to reach room temperature and stirred for 16 h then quenched with water (100 mL) and petrol/ether (1:1, 2×100 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 gel eluting with petrol/ether (20:1) gave an oil, (*S*)-2,2-dimethyl-4-((*E*/*Z*)-(*R*)-1-methylheptadec-3-enyl)[1,3]dioxolane (7.42 g, 67%) as a mixture of two isomers in ratio ca. 2:1. Palladium on charcoal (10%, 0.5 g) was added to a stirred solution of the alkenes (6.40 g, 18.1 mmol) in ethanol (100 mL). The mixture was stirred under hydrogen at atmospheric pressure. When no more hydrogen was absorbed it was filtered through a bed of Celite and washed with warm ethyl acetate (100 mL). The filtrate was evaporated at 14 mmHg to give the *title* compound **12** as a colourless oil (5.9 g, 92%), $[\alpha]_D^{22}$ +17.6 (*c* 0.625, $CHCl_3$) [Found $(M+H)^+$: 355.3582, $C_{23}H_{47}O_2$ requires: 355.3571], which showed δ_H (500 MHz, $CDCl_3$): 3.99 (1H, t, *J* 6.6 Hz), 3.86 (1H, br q, *J* 6.9 Hz), 3.59 (1H, br t, *J* 7.6 Hz), 1.56–1.51 (1H, m), 1.4 (3H, s), 1.35 (3H, s), 1.31–1.26 (30H, br s), 0.96 (3H, d, *J* 6.6 Hz), 0.88 (3H, t, *J* 6.3 Hz); δ_C (125 MHz, $CDCl_3$): 108.5, 80.4, 67.8, 36.5, 32.7, 31.9, 29.9, 29.7, 29.65, 29.6, 29.4, 27.0, 26.6, 25.5, 22.7, 15.6, 14.1; ν_{max}: 2984, 2923, 2854, 1466, 1378, 1214, 1161, 1066 cm^{-1}.

4.1.2. Methyl (E)-(R)-4-methyleicos-2-enoate.

(a) Periodic acid (11.5 g, 60.8 mmol) was added to a stirred solution of dioxolane **12** (9.0 g, 25 mmol) in dry ether (250 mL) under nitrogen at room temperature. The mixture was stirred for 16 h, then filtered through a bed of Celite and washed with ether. The solvent was evaporated to give a residue. Column chromatography eluting with petrol/ether (10:1) gave (*R*)-2-methyloctadecanal **13** as a colourless oil (5.4 g, 77%),[33] $[\alpha]_D^{25}$ −11.4 (*c* 1.07, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.6 (1H, d, *J* 1.9 Hz), 2.34–2.27 (1H, m), 1.71–1.64 (1H, m), 1.34–1.25 (29H, br s), 1.08 (3H, d, *J* 7.25 Hz), 0.87 (3H, t, *J* 6.95 Hz); δ_C (125 MHz, $CDCl_3$): 205.3, 46.3, 31.9, 30.5, 29.7, 29.66, 29.63, 29.6, 29.5, 29.4, 26.9, 22.7, 14.1, 13.3; ν_{max}: 2925, 2853, 2699, 1730, 1465.5, 1376 cm^{-1}.

(b) Methyl (triphenylphosphoranylidene) acetate (6.0 g, 18 mmol) was added in portions to a stirred solution of aldehyde **13** (4.69 g, 16.6 mmol) in toluene (75 mL) at 10 °C. The mixture was allowed to reach room temperature and stirred for 24 h. The solvent was evaporated and the residue was heated under reflux with petrol/ether (1:1, 150 mL) for 10 min. The precipitate was filtered and washed with petrol/ether (10:1, 150 mL). The filtrate was evaporated to give a residue. Chromatography on silica gel eluting with petrol/ethyl acetate (20:1) gave the *title* compound as a colourless oil (3.6 g, 65%) [Found $(M+H)^+$: 339.3269, $C_{22}H_{43}O_2$ requires: 339.3258], $[\alpha]_D^{24}$ −18.6 (*c* 1.5, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 6.86 (1H, dd, *J* 7.9, 15.5 Hz), 5.77 (1H, dd, *J* 1.0, 15.5 Hz), 3.72 (3H, s), 2.28 (1H, sept., *J* 7 Hz), 1.39–1.25 (30H, m, including br s at 1.25), 1.03 (3H, d, *J* 6.7 Hz), 0.87 (3H, t, *J* 6.9 Hz); δ_C (125 MHz, $CDCl_3$): 167.3, 155.0, 119.1, 51.3, 36.5, 36.0, 31.9, 29.7, 29.63, 29.6, 29.5, 29.3, 27.2, 22.7, 19.4, 14.1; ν_{max}: 2924, 2853, 2360, 1730, 1656, 1465, 1270, 1173, 1038 cm^{-1}.

4.1.3. (E)-(R)-4-Methyleicos-2-en-1-ol ***14***. DIBAL-H (64.8 mL, 64.8 mmol, 1 M in hexane) was added to a stirred solution of methyl (*E*)-(*R*)-4-methyleicos-2-enoate (8.47 g, 25.9 mmol) in dry dichloromethane (250 mL) at −60 °C under nitrogen. The mixture was stirred overnight at room temperature and then quenched by adding satd aq ammonium chloride (30 mL) at −30 °C, then allowed to reach room temperature and stirred for 0.5 h. Subsequently, hydrochloric acid (5%) was added until the solution became acidic. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×150 mL). The combined organic layers were dried and evaporated to give a pale yellow oil; column chromatography eluting with petrol/ether (5:2) gave a white solid, the *title* compound **14** (7.4 g, 95%), mp: 34–35 °C [Found $(M)^+$: 310.3296, $C_{21}H_{42}O$ requires: 310.3235], $[\alpha]_D^{26}$ −15 (*c* 1.4, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 5.62–5.57 (2H, m), 4.09 (2H, d, *J* 5.1 Hz), 2.17–2.07 (1H, m), 1.31–1.26 (31H, br s), 0.98 (3H, d, *J* 6.9 Hz), 0.88 (3H, t, *J* 7.0 Hz); δ_C (125 MHz, $CDCl_3$): 139.4, 127.0, 63.9, 36.8, 36.3, 31.9, 29.8, 29.7, 29.67, 29.6, 29.3, 27.3, 22.7, 20.3, 14.1; ν_{max}: 3448, 2954, 2924, 2854, 1644, 1462, 1377 cm^{-1}.

4.1.4. [(2R,3R)-3-((R)-1-Methylheptadecyl)oxiranyl]methanol ***15***. Titanium tetraisopropoxide in dry dichloromethane (3.4 M, 0.28 mL, 0.96 mmol) was added to a stirred solution of D-(−)-diethyl tartrate (0.23 mL, 1.13 mmol) in dry dichloromethane (100 mL) under nitrogen at −20 °C in the presence of 4 Å molecular sieves (0.5 g). The mixture was stirred at −20 °C for 0.5 h then *tert*-butyl hydroperoxide in dry dichloromethane (3.3 M, 4.8 mL, 16 mmol) was added dropwise and the mixture was stirred for another 0.5 h. To this solution, (*E*)-(*R*)-4-methyl-eicos-2-en-1-ol (2.5 g, 8.1 mmol) in dry dichloromethane (10 mL) was added dropwise. After stirring at the same temperature for 4.5 h, the reaction was left at −20 °C overnight, then quenched with water (10 mL) and allowed to reach room temperature. After stirring for 50 min, a solution of sodium hydroxide (30%) in satd aq sodium chloride (6 mL) was added. The mixture was stirred for 0.5 h, the organic layer was separated and the aqueous layer was re-extracted with dichloromethane (3×15 mL). The combined organic layers were dried and evaporated to give a thick oil; chromatography eluting with petrol/ether (5:2) gave the *title* compound **15** as a white solid (1.74 g, 67%), mp: 35–37 °C [Found $(M+H)^+$: 327.3274, $C_{21}H_{43}O_2$ requires: 327.3258], $[\alpha]_D^{28}$ +18.1 (*c* 0.8, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.9 (1H, ddd, *J* 2.5, 5.6, 12.6 Hz), 3.6 (1H, ddd, *J* 4.5, 7.0, 12.0 Hz), 2.94–2.92 (1H, m), 2.76 (1H, dd, *J* 2.2, 7.3 Hz), 1.53–1.48 (1H, m), 1.43–1.25 (31H, br m, including br s at 1.25), 0.92 (3H, d, *J* 7.0 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 61.9, 60.6, 57.0, 35.3, 34.5, 31.9, 29.9, 29.7, 29.63, 29.6, 29.3, 26.8, 22.7, 15.8, 14.1; ν_{max}: 3431, 2922, 2852, 1384 cm^{-1}.

4.1.5. [(2S,3S)-3-((R)-1-Methylheptadecyl)oxiranyl]methanol ***16***. Titanium tetraisopropoxide in dry dichloromethane (3.4 M, 0.28 mL, 0.96 mmol) was added to a stirred solution of L-(+)-diethyl tartrate (0.23 mL, 1.113 mmol) in dry dichloromethane (70 mL) under nitrogen at −20 °C in the presence of 4 Å molecular sieves (0.5 g). The mixture was stirred at −20 °C for 0.5 h then *tert*-butyl hydroperoxide in dry dichloromethane (3.3 M, 4.8 mL, 16 mmol) was added dropwise and the mixture was stirred for another 0.5 h. To this solution, (*E*)-(*R*)-4-methyl-eicos-2-en-1-ol (2.5 g, 8.1 mmol) in dry dichloromethane (10 mL) was added dropwise. After stirring at the same temperature for 4.5 h, the mixture was left at −20 °C for 16 h in the freezer, then quenched with water (10 mL) and allowed to reach room temperature. After stirring for 50 min, a solution of sodium hydroxide (30%) in satd aq sodium chloride (6 mL) was

added. After a further 0.5 h, the organic layer was separated and the aqueous layer was extracted with dichloromethane (3×15 mL). The combined organic layers were dried and evaporated to give a thick oil; column chromatography eluting with petrol/ether (5:2) gave a white solid, the *title* compound **16** (2.0 g, 75%), mp: 48–49 °C [Found $(M+H)^+$: 327.3258, $C_{21}H_{43}O_2$ requires: 327.3258], $[\alpha]_D^{22}$ −21.2 (*c* 1.56, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.88 (1H, ddd, *J* 2.2, 5.7, 12.6 Hz), 3.58–3.53 (1H, m), 2.94 (1H, br pent., *J* 2.5 Hz), 2.68 (1H, dd, *J* 2.6, 7.3 Hz), 2.59 (1H, br t, *J* 6.3 Hz), 1.38–1.19 (31H, br m, including br s at 1.23), 0.98 (3H, d, *J* 6.6 Hz), 0.85 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 61.8, 60.6, 58.5, 35.4, 33.6, 31.9, 29.8, 29.6, 29.59, 29.58, 29.5, 29.3, 27.1, 22.6, 17.1, 14.0; ν_{max}: 3430, 2918, 2849, 1463, 1384, 1071 cm^{-1}.

*4.1.6. (2S,3R)-3-((R)-1-Methylheptadecyl)-oxirane-2-carbaldehyde **17**.* Alcohol **15** (1.23 g, 3.76 mmol) in dichloromethane (15 mL) was added to a stirred suspension of pyridinium chlorochromate (2.0 g, 7.5 mmol) in dichloromethane (100 mL) at room temperature.[48] The mixture was stirred vigorously for 3 h, diluted with ether (100 mL), filtered through a bed of Celite, then washed well with ether and the filtrate evaporated to give a residue. Chromatography on silica gel eluting with petrol/ether (5:2) gave a white solid, the *title* compound **17** (0.72 g, 60%), mp: 40–42 °C, $[\alpha]_D^{28}$ −63.5 (*c* 1.06, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.02 (1H, d, *J* 6.3 Hz), 3.14 (1H, dd, *J* 1.9, 6.3 Hz), 3.05 (1H, dd, *J* 1.9, 6.6 Hz), 1.55–1.48 (1H, m), 1.43–1.22 (30H, br m, including br s at 1.26), 0.95 (3H, d, *J* 6.9 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 198.6, 61.3, 57.9, 35.3, 34.4, 31.9, 29.74, 29.7, 29.64, 29.6, 29.5, 29.3, 26.8, 22.7, 15.6, 14.1; ν_{max}: 2918, 2851, 1741, 1384 cm^{-1}, and recovered starting material (0.25 g).

*4.1.7. (2R,3S)-3-((R)-1-Methylheptadecyl)-oxirane-2-carbaldehyde **18**.* Alcohol **16** (1.96 g, 6.01 mmol) in dichloromethane (15 mL) was added to a stirred suspension of pyridinium chlorochromate (3.9 g, 18 mmol) in dichloromethane (100 mL) at room temperature. The mixture was stirred vigorously for 3 h then diluted with ether (100 mL), filtered through a bed of Celite, then washed with ether and the filtrate evaporated to give a residue. Chromatography on silica gel eluting with petrol/ether (5:2) gave a white solid, the *title* compound **18** (1.2 g, 59%), mp: 31–32 °C, $[\alpha]_D^{20}$ +53.5 (*c* 1.22, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.02 (1H, d, *J* 6.3 Hz), 3.19 (1H, dd, *J* 1.9, 6.3 Hz), 3.02 (1H, dd, *J* 1.9, 7.0 Hz), 1.51–1.46 (1H, br pent., *J* 6.6 Hz), 1.41–1.22 (30H, br m), 1.06 (3H, d, *J* 6.6 Hz), 0.88 (3H, t, *J* 6.7 Hz); δ_C (125 MHz, $CDCl_3$): 198.5, 61.2, 59.0, 35.3, 33.3, 31.9, 29.7, 29.68, 29.64, 29.62, 29.6, 29.5, 29.4, 27.0, 22.7, 16.9, 14.1; ν_{max}: 2954, 2924, 2854, 1734, 1462, 1377 cm^{-1}. Starting material (0.55 g) was recovered.

*4.1.8. (2S,3S)-2-(13-Bromotridecyl)-3-((R)-1-methylheptadecyl)oxirane **20**.* Lithium bis(trimethylsilyl)amide (5.4 mL, 5.7 mmol, 1.06 M) was added dropwise with stirring to aldehyde **18** (0.95 g, 2.9 mmol) and 5-(12-bromo-dodecane-1-sulfonyl)-1-phenyl-1*H*-tetrazole **19** (see Supplementary data) (1.74 g, 3.80 mmol) in dry tetrahydrofuran (50 mL) under nitrogen at −10 °C. The mixture was allowed to reach room temperature, stirred for 1 h, then quenched with water (7 mL) and petrol/ether (1:1, 40 mL). The organic layer was separated and the aqueous layer was re-extracted with petrol/ether (1:1, 2×20 mL). The combined organic layers were washed with satd aq sodium chloride (2×20 mL), dried and evaporated to give a thick oil. Chromatography on silica gel eluting with petrol/ether (20:1) gave a white solid (*E*/*Z*)-(2*S*,3*S*)-2-(13-bromotridec-1-enyl)-3-((*R*)-1-methylheptadecyl)oxirane (1.16 g, 71%), as a 1.6:1 mixture of two isomers. Hydrogenation was carried out with dipotassium azodicarboxylate as before. Chromatography eluting with petrol/ether (20:1) gave a white solid, the *title* compound **20** (0.64 g, 93%), mp: 42–44 °C [Found $(M+Na)^+$: 579.36, $C_{33}H_{65}NaBrO$ requires: 579.41], $[\alpha]_D^{26}$ −13.1 (*c* 1.2, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.41 (2H, t, *J* 7.0 Hz), 2.71 (1H, dt, *J* 2.2, 5.4 Hz), 2.41 (1H, dd, *J* 1.9, 7.0 Hz), 1.85 (2H, pent., *J* 6.9 Hz), 1.54–1.22 (53H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.0 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 63.8, 58.8, 36.0, 34.0, 33.8, 32.8, 32.3, 31.9, 29.9, 29.7, 29.63, 29.6, 29.56, 29.54, 29.53, 29.5, 29.4, 29.36, 28.8, 28.2, 27.2, 26.1, 22.7, 22.6, 17.3, 14.1; ν_{max}: 2919, 2850, 1462, 1377, 1116 cm^{-1}.

*4.1.9. 5-(13-[(2S,3S)-3-((R)-1-Methylheptadecyl)oxiranyl]tridecane-1-sulfonyl)-1-phenyl-1H-tetrazole **21**.*

(i) (2*S*,3*S*)-2-(13-Bromotridecyl)-3-((*R*)-1-methylheptadecyl)-oxirane **20** (0.8 g, 1.4 mmol) was added with vigorous stirring to 1-phenyl-1*H*-tetrazole-5-thiol (0.25 g, 1.43 mmol) and anhydrous potassium carbonate (0.390 g, 2.86 mmol) in acetone (50 mL). The mixture was heated under reflux for 2.5 h when the inorganic salts were filtered off and washed with acetone; the solution was evaporated to a small bulk and the residue extracted between dichloromethane (30 mL) and water (30 mL). The aqueous layer was extracted with dichloromethane (2×20 mL). The combined organic phases were washed with water (25 mL), dried and evaporated to give a solid. Chromatography on silica gel eluting with petrol/ethyl acetate (10:1) gave a white solid, 5-(13-[(2*S*,3*S*)-3-((*R*)-1-methyl-heptadecyl)oxiranyl]tridecylsulfanyl)-1-phenyl-1*H*-tetrazole (0.77 g, 82%), mp: 41–43 °C [Found $(M+H)^+$: 655.5341, $C_{40}H_{71}N_4OS$ requires: 655.5343], $[\alpha]_D^{20}$ −12.5 (*c* 1.09, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.60–7.52 (5H, m), 3.40 (2H, t, *J* 7.6 Hz), 2.71 (1H, dt, *J* 2.2, 5.7 Hz), 2.41 (1H, dd, *J* 2.2, 7.3 Hz), 1.82 (2H, br pent., *J* 7.6 Hz), 1.54–1.26 (53H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.3 Hz), 0.88 (3H, t, *J* 6.7 Hz); δ_C (125 MHz, $CDCl_3$): 154.5, 133.8, 130.0, 129.7, 123.9, 63.8, 58.8, 36.0, 33.8, 33.4, 32.3, 31.9, 29.9, 29.7, 29.66, 29.64, 29.63, 29.6, 29.56, 29.53, 29.5, 29.4, 29.3, 29.1, 29.0, 28.6, 27.2, 26.1, 22.7, 17.3, 14.1; ν_{max}: 2954, 2924, 2854, 1501, 1462, 1377 cm^{-1}.

(ii) Ammonium molybdate (VI) tetrahydrate (0.60 g, 0.53 mmol) in H_2O_2 (35%, w/w, 1.5 mL) was added to a stirred solution of 5-(13-[(2*S*,3*S*)-3-((*R*)-1-methylheptadecyl)oxiranyl]tridecylsulfanyl)-1-phenyl-1*H*-tetrazole (0.78 g, 1.19 mmol) in THF (15 mL) and IMS (25 mL) at 12 °C and stirred at rt for 2 h. Further ammonium molybdate (VI) tetrahydrate (0.60 g, 0.53 mmol) in ice cold H_2O_2 (35%, w/w, 1.5 mL) was added and the mixture was stirred at rt 18 h, then poured into water (75 mL) and extracted with dichloromethane (3×40 mL). The combined organic phases were washed with water (2×25 mL), dried and evaporated to give a solid. Chromatography on silica gel eluting with petrol/ethyl acetate (10:1) gave a white solid of the *title* compound **21** (0.70 g, 67%), mp: 45–47 °C [Found $(M+Na)^+$: 709.5018, $C_{40}H_{70}N_4NaO_3S$ requires: 709.5061], $[\alpha]_D^{20}$ −8.5 (*c* 0.97, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 7.72–7.69 (2H, m), 7.66–7.59 (3H, m), 3.73 (2H, t, *J* 7.9 Hz), 2.72 (1H, dt, *J* 2.2, 5.7 Hz), 2.41 (1H, dd, *J* 2.2, 7.0 Hz), 1.99–1.93 (2H, m), 1.56–1.26 (53H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.3 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (500 MHz, $CDCl_3$): 153.5, 133.1, 131.4, 129.7, 125.0, 63.8, 58.8, 56.0, 36.0, 33.8, 32.3, 31.9, 29.9, 29.7, 29.64, 29.63, 29.6, 29.55, 29.53, 29.5, 29.4, 29.3, 29.2, 28.9, 28.1, 27.2, 26.1, 22.7, 21.9, 17.3, 14.1; ν_{max}: 2918, 2851, 1498, 1464, 1344, 1153 cm^{-1}.

*4.1.10. 5-(13-[(2R,3R)-3-((R)-1-Methylheptadecyl)-oxiranyl]-tridecane-1-sulfonyl)-1-phenyl-1H-tetrazole **22**.* Ammonium molybdate (VI) tetrahydrate (0.4 g, 0.322 mmol) in ice cold H_2O_2 (35% w/w, 1 mL) was added to a stirred solution of 5-(13-[(2*R*,3*R*)-3-((*R*)-1-methylheptadecyl)oxiran-yl]-tridecylsulfanyl)-1-phenyl-1*H*-

tetrazole (see Supplementary data) (0.47 g, 0.72 mmol) in THF (10 mL) and IMS (15 mL) at 12 °C and stirred at rt for 2 h. Further ammonium molybdate (VI) tetrahydrate (0.40 g, 0.32 mmol) in ice cold H_2O_2 (35%, w/w, 1 mL) was added and the mixture was stirred at rt for 18 h, then poured into water (50 mL) and extracted with dichloromethane (3×25 mL). The combined organic phases were washed with water (2×15 mL), dried and evaporated to give a solid; chromatography on silica gel eluting with petrol/ethyl acetate (10:1) gave a white solid, the *title* compound **22** (0.34 g, 69%), mp: 41–42 °C [Found $(M+H)^+$: 687.5243, $C_{40}H_{71}N_4O_3S$ requires: 687.5241], $[\alpha]_D^{20}$ +6.25 (*c* 1.3, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 7.72–7.68 (2H, m), 7.64–7.57 (3H, m), 3.72 (2H, t, *J* 7.9 Hz), 2.66 (1H, dt, *J* 1.9, 5.7 Hz), 2.45 (1H, dd, *J* 2.3, 7.3 Hz), 1.98–1.91 (2H, m), 1.58–1.25 (53H, br m, including br s at 1.25), 0.91 (3H, d, *J* 6.6 Hz), 0.87 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 153.5, 133.0, 131.4, 129.6, 125.0, 63.7, 57.4, 56.0, 35.8, 34.6, 32.2, 31.9, 29.9, 29.7, 29.6, 29.57, 29.55, 29.52, 29.5, 29.47, 29.4, 29.3, 29.1, 28.8, 28.1, 26.8, 26.1, 22.6, 21.9, 15.9, 14.1; ν_{max}: 2921, 2853, 1500, 1463, 1377, 1344, 1153, 1049 cm^{-1}.

4.1.11. Methyl 15-(1-phenyl-1H-tetrazole-5-sulfonyl)-pentadecanoate ***26***.

(i) Methyl 15-bromopentadecanoate (see Supplementary data) (20.6 g, 61.5 mmol) was added with vigorous stirring to 1-phenyl-1*H*-tetrazole-5-thiol (10.95 g, 61.49 mmol) and anhydrous potassium carbonate (17.0 g, 123 mmol) in acetone (250 mL). The mixture was heated under reflux for 2.5 h then worked up and purified as before to give methyl 15-(1-phenyl-1*H*-tetrazole-5-ylsulfanyl)pentadecanoate as a white solid (24 g, 90%), mp: 62–64 °C [Found $(M+Na)^+$: 455.2448, $C_{23}H_{36}N_4NaO_2S$ requires: 455.2451], which showed δ_H (500 MHz, $CDCl_3$): 7.75–7.60 (5H, m), 3.67 (3H, s), 3.39 (2H, t, *J* 7.3 Hz), 2.30 (2H, t, *J* 7.6 Hz), 1.82 (2H, quintet, *J* 7.4 Hz), 1.62 (2H, quintet, *J* 7.4 Hz), 1.47–1.41 (2H, m), 1.32–1.25 (18H, m); δ_C (125 MHz, $CDCl_3$): 174.3, 154.5, 133.8, 130.1, 129.8, 123.9, 51.4, 34.1, 33.4, 29.6, 29.56, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.6, 25.0; ν_{max}: 2916, 2850, 1742, 1499, 1472, 1250, 1171 cm^{-1}.

(ii) A solution of ammonium molybdate (VI) tetrahydrate (30.9 g, 25.0 mmol) in H_2O_2 (35% w/w, 70 mL) was added to a stirred solution of methyl 15-(1-phenyl-1*H*-tetrazole-5-ylsulf-anyl) pentadecanoate (24.0 g, 55.5 mmol) in THF (300 mL) and IMS (500 mL) at 12 °C and stirred at rt for 2 h. Further ammonium molybdate (VI) tetrahydrate (13.0 g, 10.5 mmol) in H_2O_2 (35%, w/w, 35 mL) was added and the mixture was stirred at rt for 18 h, then worked up and purified as before to give the *title* compound **26** as a white solid (23.6 g, 91%), mp: 72–73 °C [Found $(M+Na)^+$: 487.2343, $C_{23}H_{36}N_4NaO_4S$ requires: 487.2349], which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.68 (2H, m), 7.63–7.58 (3H, m), 3.73 (2H, distorted t, *J* 8.2 Hz), 3.67 (3H, s), 2.30 (2H, t, *J* 7.6 Hz), 1.98–1.92 (2H, m), 1.64–1.58 (2H, m), 1.52–1.46 (2H, m), 1.34–1.25 (18H, m); δ_C (125 MHz, $CDCl_3$): 174.3, 153.5, 133.0, 131.4, 129.9, 129.7, 125.0, 124.98, 56.0, 51.4, 34.1, 29.54, 29.53, 29.51, 29.5, 29.4, 29.2, 29.15, 28.9, 28.1, 25.0, 21.9; ν_{max}: 2918, 2948, 1729, 1497, 1464, 1343, 1255, 1199, 1157 cm^{-1}.

4.1.12. Methyl (R)-18-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-nonadecanoate ***28***. Lithium bis(trimethylsilyl)amide (27.8 mL, 29.5 mmol,1.06 M) was added dropwise with stirring to (*R*)-3-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-butyraldehyde **27**[28,34,35] (3.0 g, 17 mmol) and sulfone **26** (10.5, 22.7 mmol) in dry THF (150 mL) under nitrogen at −10 °C. The mixture was allowed to reach rt and stirred for 1 h, then quenched with water (80 mL) and petrol/ethyl acetate (1:1, 80 mL). 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 washed with satd aq sodium chloride (2×80 mL), dried and evaporated to give a thick oil. Chromatography on silica gel eluting with petrol/ethyl acetate (20:1) gave a thick oil, methyl (*E,Z*)-(*R*)-18-((*S*)-2,2-dimethyl[1,3] dioxolan-4-yl)-nonadec-15-enoate (4.4 g, 61%) as a mixture of two isomers in ratio 2:1. Palladium 10% on carbon (1 g) was stirred with the alkenes (4.40 g, 10.7 mmol) in ethanol (100 mL) and THF (20 mL) under hydrogen for 2 h until no more hydrogen was absorbed. The solution was filtered through a bed of Celite and the solvent was evaporated to give a white solid, the *title* compound **28** (4.15, 93%), mp: 36–38 °C [Found $(M+Na)^+$: 435.3387, $C_{25}H_{48}NaO_4$ requires: 435.3450], $[\alpha]_D^{20}$ +11.3 (*c* 1.50, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.0 (1H, br q, *J* 6.3 Hz), 3.86 (1H, br q, *J* 7.3 Hz), 3.66 (3H, s), 3.59 (1H, br t, *J* 7.6 Hz), 2.30 (2H, t, *J* 7.6 Hz), 1.61 (1H, pent., *J* 7.3 Hz), 1.57–1.53 (2H, m), 1.40 (3H, s), 1.35 (3H, s), 1.28–1.21 (27H, br s), 1.10–1.06 (1H, m), 0.96 (3H, d, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 174.3, 108.5, 80.4, 67.8, 51.4, 36.5, 34.1, 32.7, 29.8, 29.64, 29.62, 29.6, 29.57, 29.4, 29.2, 29.1, 27.0, 26.6, 25.5, 24.9, 15.6; ν_{max}: 2922, 2853, 1736, 1463, 1377, 1213, 1169, 1051 cm^{-1}.

4.1.13. (R)-18-((S)-2,2-Dimethyl[1,3]dioxolan-4-yl)-nonadecan-1-ol ***29***. (*R*)-18-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)nonadecanoic acid methyl ester (4.0 g, 9.7 mmol) in THF (30 mL) was added dropwise over 15 min to a suspension of lithium aluminium hydride (0.560 g, 14.5 mmol) in THF (100 mL) at rt. The mixture was heated under reflux for 1 h, then cooled to rt 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 bed of Celite and washed with THF (100 mL). The filtrate was evaporated to give a residue, which was purified by chromatography on silica gel eluting with petrol/ethyl acetate (2:1) to give a white solid, the *title* compound **29** (3.4 g, 91%), mp: 56–57 °C [Found $(M+H)^+$: 385.3678, $C_{24}H_{49}O_3$ requires: 385.3678], $[\alpha]_D^{18}$ +17.6 (*c* 1.10, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.99 (1H, dd, *J* 3.6, 7.9 Hz), 3.86 (1H, br q, *J* 6.9 Hz), 3.63 (2H, t, *J* 6.6 Hz), 3.59 (1H, t, *J* 7.9 Hz), 2.1 (1H, s), 1.59–1.51 (4H, m), 1.39 (3H, s), 1.34 (3H, s), 1.32–1.21 (28H, br m, including br s at 1.25), 1.11–1.03 (1H, m), 0.95 (3H, d, *J* 6.9 Hz); δ_C (125 MHz, $CDCl_3$): 108.5, 80.4, 67.8, 63.0, 36.5, 32.8, 32.7, 29.8, 29.64, 29.63, 29.6, 29.58, 29.4, 27.0, 26.6, 25.7, 25.5, 15.6; ν_{max}: 3448, 2961, 2923, 2852, 1465, 1377, 1155, 1056 cm^{-1}.

4.1.14. (S)-4-((R)-18-Bromo-1-methyloctadecyl)-2,2-dimethyl-[1,3] dioxolane ***30***. *N*-Bromosuccinimide (2.04 g, 11.5 mmol) was added in portions over 15 min to a stirred solution of (*R*)-18-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)nonadecan-1-ol (3.4 g, 8.9 mmol), triphenylphosphine (2.89 g, 11.1 mmol) and sodium hydrogen carbonate (0.2 g) in dichloromethane (70 mL) at 0 °C. The mixture was stirred at rt for 1 h, then quenched with satd aq sodium *meta*-bisulfite (50 mL). The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×50 mL). The combined organic extracts were washed with water (50 mL), dried and evaporated to give a residue. This was heated under reflux for 30 min with ether (150 mL) and then filtered and washed with petrol/ethyl acetate (5:1, 50 mL). The filtrate was evaporated and the residue was purified by column chromatography eluting with petrol/ethyl acetate (5:1) to give a colourless oil, the *title* compound **30** (3.8 g, 96%) [Found M^+: 447.2831, $C_{24}H_{47}Br^{79}O_2$ requires: 447.2832], $[\alpha]_D^{18}$ +16.5 (*c* 1.1, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.98 (1H, dd, *J* 6.0, 7.6 Hz), 3.85 (1H, q, *J* 7.3 Hz), 3.58 (1H, t, *J* 7.6 Hz), 3.38 (2H, t, *J* 6.9 Hz), 1.84 (2H, pent., *J* 7.0 Hz), 1.59–1.51 (1H, m), 1.44–1.40 (2H, m), 1.38 (3H, s), 1.33 (3H, s), 1.31–1.2 (27H, br m, including br s at 1.25), 1.0–1.03 (1H, m), 0.95 (3H, d, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 108.4, 80.4, 67.8, 36.5, 33.7, 32.8, 32.77, 29.8,

29.6, 29.57, 29.5, 29.4, 28.7, 28.2, 27.0, 26.6, 25.5, 15.6; ν_{max}: 2985, 2921, 2851, 1470, 1377, 1369, 1250, 1216, 1160, 1056 cm^{-1}.

*4.1.15. 5-[(R)-18-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl)nonadecane sulfonyl]-1-phenyl-1H-tetrazole **31**.*

(i) (*S*)-4-((*R*)-18-Bromo-1-methyloctadecyl)-2,2-dimethyl-[1,3] dioxolane (3.8 g, 8.5 mmol) was added with vigorous stirring to 1-phenyl-1*H*-tetrazole-5-thiol (1.5 g, 8.5 mmol) and anhydrous potassium carbonate (2.34 g, 17.0 mmol) in acetone (100 mL). The mixture was heated under reflux for 2.5 h, then worked up and purified by chromatography on silica gel eluting with petrol/ethyl acetate (8:2) to give a yellow oil, 5-[(*R*)-18-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)nonadecylsulfan-yl]-1-phenyl-1*H*-tetrazole (4.2 g, 90%) [Found $(M+H)^+$: 545.3860, $C_{31}H_{53}N_4O_2S$ requires: 545.3884], $[\alpha]_D^{20}$ +12.6 (*c* 1.46, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.58–7.49 (5H, m), 3.98 (1H, dd, *J* 6.3, 7.5 Hz), 3.85 (1H, q, *J* 7.0 Hz), 3.58 (1H, t, *J* 7.6 Hz), 3.37 (2H, t, *J* 7.3 Hz), 1.80 (2H, pent., *J* 7.3 Hz), 1.58–1.50 (1H, m), 1.45–1.41 (2H, m), 1.38 (3H, s), 1.30 (3H, s), 1.29–1.2 (27H, br m, including br s at 1.24), 1.11–1.02 (1H, m), 0.94 (3H, d, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 154.4, 133.8, 129.9, 129.7, 123.8, 108.4, 80.3, 67.7, 36.4, 33.4, 32.7, 29.8, 29.6, 29.55, 29.5, 29.46, 29.4, 29.1, 29.0, 28.6, 26.9, 26.6, 25.5, 15.5; ν_{max}: 2983, 2924, 2853, 1598, 1500, 1464, 1379, 1245, 1064 cm^{-1}.

(ii) Ammonium molybdate (IV) tetrahydrate (4.0 g, 3.3 mmol) in ice cold H_2O_2 (35% w/w, 10 mL) was added to a stirred solution of the above tetrazole (4.0 g, 7.3 mmol) in IMS (100 mL) and THF (10 mL) at 12 °C and stirred at rt for 2 h. Further ammonium molybdate (IV) tetrahydrate (4.0 g, 3.3 mmol) in ice cold H_2O_2 (35% w/w, 10 mL) was added and the mixture was stirred at rt for 18 h, then worked up and purified by chromatography on silica gel eluting with petrol/ethyl acetate (8:2) to give a white solid, the *title* compound **31** (3.9 g, 92%), mp: 52–54 °C [Found $(M+Na)^+$: 599.3632, $C_{31}H_{52}N_4NaO_4S$ requires: 599.3606], $[\alpha]_D^{20}$ +12.5 (*c* 1.10, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.70–7.68 (2H, m), 7.64–7.58 (3H, m), 4.0 (1H, dd, *J* 6.3, 7.9 Hz), 3.87 (1H, q, *J* 7.0 Hz), 3.73 (2H, t, *J* 7.9 Hz), 3.60 (1H, t, *J* 7.9 Hz), 1.98–1.92 (2H, m), 1.58–1.54 (1H, m), 1.52–1.47 (2H, m), 1.40 (3H, s), 1.35 (3H, s), 1.33–1.22 (27H, br m, including br s at 1.26), 1.11–1.07 (1H, m), 0.96 (3H, d, *J* 6.7 Hz); δ_C (125 MHz, $CDCl_3$): 153.6, 133.2, 131.4, 129.7, 125.1, 108.5, 80.4, 67.8, 56.1, 36.5, 32.8, 29.9, 29.64, 29.61, 29.6, 29.5, 29.4, 29.2, 28.9, 28.1, 27.0, 26.6, 25.5, 22.0, 15.6; ν_{max}: 2921, 2853, 1460, 1377, 1149, 1066 cm^{-1}.

*4.1.16. Methyl (2R,3R,23R)-3-(tert-butyldimethylsilanyloxy)-23-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)-2-docosyl-tetracosanoate **33**.* Lithium bis(trimethylsilyl)amide (9.0 mL, 9.6 mmol, 1.06 M) was added dropwise with stirring to methyl (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-3-oxopropyl]tetracosanoate **32** (3.5 g, 6.15 mmol)[28,31] and sulfone **31** (4.26 g, 7.38 mmol) in dry THF (50 mL) under nitrogen at −10 °C. The mixture was allowed to reach rt and stirred for 2 h, then quenched with water (50 mL) and petrol/ethyl acetate (1:1, 50 mL). The aqueous layer was re-extracted with petrol/ethyl acetate (1:1, 2×50 mL). The combined organic layers were washed with satd aq sodium chloride (2×50 mL), dried and evaporated to give a thick oil. Chromatography eluting with petrol/ethyl acetate (20:1) gave a colourless oil, methyl (*E*/*Z*)-(2*R*,3*R*,23*R*)-3-(*tert*-butyldimethylsilanyloxy)-23-((*S*)-2,2-dimethyl[1.3]dioxolan-4-yl)-2-docosyltetracos-5-enoate (4.4 g, 89%) as a mixture of two isomers in ratio 2:1. Palladium on carbon (10%, 1.5 g) was added to a stirred solution of the alkenes (4.0 g, 4.0 mmol) in IMS (30 mL) and THF (10 mL) under hydrogen atmosphere. Hydrogenation was carried out for 2 h then the mixture was filtered through a bed of Celite and the solvent was evaporated. Column chromatography eluting with petrol/ethyl acetate (20:1) gave a colourless oil, the *title* compound **33** (3.53 g, 95%) [Found $(M+Na)^+$: 943.8484, $C_{58}H_{116}NaO_5Si$ requires: 943.8489], $[\alpha]_D^{20}$ +4.41 (*c* 1.62, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.0 (1H, dd, *J* 6.3, 7.6 Hz), 3.92–3.90 (1H, m), 3.87 (1H, br q, *J* 7.0 Hz), 3.65 (3H, s), 3.60 (1H, br t, *J* 7.9 Hz), 2.52 (1H, ddd, *J* 3.8, 7.3, 11.0 Hz), 1.59–1.53 (2H, m), 1.49–1.42 (2H, m), 1.40 (3H, s), 1.35 (3H, s), 1.29–1.22 (77H, br m, including br s at 1.26), 0.96 (3H, d, *J* 6.7 Hz), 0.88 (3H, t, *J* 7.3 Hz), 0.86 (9H, s), 0.047 (3H, s), 0.023 (3H, s); δ_C (125 MHz, $CDCl_3$): 175.1, 108.5, 80.4, 73.2, 67.8, 51.9, 51.6, 36.5, 33.7, 32.7, 31.9, 29.9, 29.8, 29.7, 29.67, 29.65, 29.6, 29.57, 29.55, 29.4, 29.35, 27.8, 27.5, 27.0, 26.6, 25.75, 25.5, 23.7, 22.7, 18.0, 15.6, 14.1, −4.37, −4.9; ν_{max}: 2924, 2853, 1740, 1464, 1377, 1368, 1253, 1165, 1067 cm^{-1}.

*4.1.17. Methyl (2R,3R,23R)-23-((S)-2,2-dimethyl[1,3]-dioxolan-4-yl)-2-docosyl-3-hydroxytetracosanoate **34**.* The ester **33** (3.85 g, 4.17 mmol) was dissolved in dry THF (50 mL) in a dry poly-ethylene vial under nitrogen at rt and stirred. Pyridine (1.5 mL) and hydrogen fluoride-pyridine complex (4 mL) were added and the mixture was stirred for 17 h at 40 °C, then poured slowly to a satd aq $NaHCO_3$ until no more carbon dioxide was liberated and the product was extracted with petrol/ethyl acetate (1:1, 3×50 mL). The combined organic layers were washed with brine and dried. The solvent was evaporated and the crude product was purified by column chromatography eluting with petrol/ethyl acetate (20:1) to give a white solid, the *title* compound **34** (2.7 g, 80%), mp: 56–58 °C [Found $(M+Na)^+$: 829.7631, $C_{52}H_{102}NaO_5$ requires: 829.7624], $[\alpha]_D^{25}$ +13.3 (*c* 1.07, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.0 (1H, dd, *J* 6.3, 7.9 Hz), 3.87 (1H, br q, *J* 7.3 Hz), 3.71 (3H, s), 3.65 (1H, br s), 3.60 (1H, br t, *J* 7.6 Hz), 2.43 (1H, dt, *J* 5.4, 10.4 Hz), 1.73–1.67 (1H, m), 1.60–1.53 (2H, m), 1.47–1.43 (2H, m), 1.40 (3H, s), 1.35 (3H, s), 1.31–1.21 (77H, br m), 0.96 (3H, d, *J* 6.7 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 176.2, 108.5, 80.4, 72.3, 67.8, 51.5, 50.9, 36.5, 35.7, 32.7, 31.9, 29.9, 29.7, 29.66, 29.62, 29.6, 29.55, 29.53, 29.5, 29.4, 29.35, 27.4, 27.0, 26.6, 25.7, 25.5, 22.7, 15.6, 14.1; ν_{max}: 3369, 2953, 2922, 2853, 1709, 1461, 1377, 1188, 1164 cm^{-1}.

*4.1.18. Methyl (2R,3R,23R)-3-acetoxy-23((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-2-docosyltetracosanoate **35**.* A mixture of acetic anhydride (10 mL) and anhydrous pyridine (10 mL) was added to stirred solution of the methyl (2*R*,3*R*, 23*R*)-23-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-2-docosyl-3-hydroxytetracosanoate (2.6 g, 3.2 mmol) in dry toluene (35 mL) at rt and stirred for 18 h, then diluted with toluene (10 mL) and the solvent was evaporated. Column chromatography eluting with petrol/ethyl acetate (10:1) gave a white solid, the *title* compound **35** (2.7 g, 98%), mp: 51–52 °C [Found $(M+Na)^+$: 871.7758, $C_{54}H_{104}NaO_6$ requires: 871.7730], $[\alpha]_D^{25}$ +15.4 (*c* 1.10, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 5.08 (1H, br dq, *J* 4.1, 8.2 Hz), 4.0 (1H, dd, *J* 6.3, 7.9 Hz), 3.87 (1H, br q, *J* 7.6 Hz), 3.68 (3H, s), 3.60 (1H, br t, *J* 7.6 Hz), 2.61 (1H, ddd, *J* 4.4, 6.9, 11.0 Hz), 2.03 (3H, s), 1.64–1.21 (80H, br m, including br s at 1.25), 1.40 (3H, s), 1.35 (3H, s), 1.11–1.04 (1H, m), 0.96 (3H, d, *J* 6.6 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 173.6, 170.3, 108.5, 80.4, 74.1, 67.8, 51.5, 49.6, 36.5, 32.7, 31.9, 31.7, 29.9, 29.7, 29.64, 29.6, 29.5, 29.42, 29.4, 29.34, 28.1, 27.5, 27.0, 26.6, 25.5, 24.98, 22.7, 21.0, 15.6, 14.1; ν_{max}: 2953, 2923, 2854, 1748, 1462, 1377, 1235, 1161 cm^{-1}.

*4.1.19. Methyl (2R,3R,23R)-3-acetoxy-2-docosyl-23-methyl-24-oxo-tetracosanoate **36**.* Periodic acid (1.8 g, 7.9 mmol) was added to a stirred solution of ester **35** (2.7 g, 3.2 mmol) in dry ether (70 mL) at rt under nitrogen. The mixture was stirred for 16 h, then filtered through a bed of Celite and washed with ether. The solvent was evaporated and the crude product was purified by column chromatography eluting with petrol/ethyl acetate (7:1) to give a white solid, the *title* compound **36** (1.6 g, 64%), mp: 41–43 °C, $[\alpha]_D^{25}$ +4.90

(*c* 1.02, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.61 (1H, d, *J* 2.2 Hz), 5.08 (1H, br dt, *J* 3.8, 7.9 Hz), 3.68 (3H, s), 2.61 (1H, ddd, *J* 4.5, 7.0, 11.1 Hz), 2.37–2.29 (1H, m), 2.03 (3H, s), 1.72–1.21 (80H, br m, including br s at 1.25), 1.09 (3H, d, *J* 7.0 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 205.4, 173.6, 170.3, 74.1, 51.5, 49.6, 46.3, 31.9, 31.7, 30.5, 29.72, 29.4, 29.39, 29.34, 28.1, 27.5, 26.9, 25.0, 22.7, 21.0, 14.1, 13.3; ν_{max}: 2923, 2852, 1745, 1465, 1371, 1236, 1165, 1022 cm^{-1}.

4.1.20. Methyl (E)-(2R,3R,23R)-3-acetoxy-23-methyl-37-[(2S,3S)-3-((R)-1-methylheptadecyl)oxiranyl]-2-docosyl-heptatri acont-24-enoate ***37***. Potassium bis(trimethylsilyl)amide (0.350 mL, 0.176 mmol, 0.5 M) was added dropwise with stirring to aldehyde **36** (0.088 mg, 0.113 mmol) and sulfone **21** (0.093 mg, 0.135 mmol) in dry 1,2-dimethoxyethane (7 mL) under nitrogen at −5 °C. The mixture was allowed to reach 10 °C, then quenched with water (5 mL) and petrol/ethyl acetate (20:1, 20 mL) was added. The aqueous layer was re-extracted with petrol/ethyl acetate (20:1, 2×15 mL). The combined organic layers were washed with satd aq sodium chloride (2×15 mL), dried and evaporated. Column chromatography eluting with petrol/ethyl acetate (20:1) gave a white solid, the *title* compound **37** (37 mg, 26%), mp: 34–35 °C [Found $(M+Na)^+$: 1260.2128, $C_{83}H_{160}NaO_5$ requires: 1260.2158], $[\alpha]_D^{18}$ −2.0 (*c* 1.0, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 5.33 (1H, br dq, *J* 6.7, 15.5 Hz), 5.24 (1H, dd, *J* 7.6, 15.5 Hz), 5.11–5.07 (1H, m), 3.68 (3H, s), 2.71 (1H, dt, *J* 2.2, 5.4 Hz), 2.62 (1H, ddd, *J* 4.1, 6.6, 10.7 Hz), 2.40 (1H, dd, *J* 5.1, 7.3 Hz), 2.03 (3H, s), 1.99–1.94 (2H, m), 1.69–1.08 (134H, br m, including br s at 1.26), 1.00 (3H, d, *J* 6.0 Hz), 0.94 (3H, d, *J* 7 Hz), 0.89 (6H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 173.6, 170.3, 136.5, 128.4, 74.1, 63.8, 58.8, 51.5, 49.6, 37.2, 36.7, 36.0, 33.8, 32.6, 32.3, 31.9, 31.7, 29.9, 29.8, 29.7, 29.66, 29.65, 29.6, 29.55, 29.53, 29.5, 29.46, 29.43, 29.4, 29.35, 29.1, 28.1, 27.5, 27.3, 27.2, 26.1, 25.0, 22.7, 21.0, 20.9, 17.3, 14.1; ν_{max}: 2919, 2851, 1737, 1470, 1238 cm^{-1}.

4.1.21. (E)-(2R,3R,23R)-3-Hydroxy-23-methyl-37-[(2S, 3S)-3-((R)-1-methylheptadecyl)-oxiranyl]-2-docosyl-heptatriacont-24-enoic acid ***38***. Lithium hydroxide monohydrate (31.8 mg, 0.759 mmol) was added to a stirred solution of ester **37** (31.4 mg, 0.0253 mmol) in THF (4 mL), methanol (0.5 mL) and water (0.5 mL) at rt. The mixture was stirred at 45 °C overnight, then cooled to rt and a mixture of petrol/ethyl acetate (7:2, 5 mL) was added. The mixture was acidified to pH 1 with potassium hydrogen sulfate. Further petrol/ethyl acetate (7:2, 10 mL) was added and the organic layer was separated. The aqueous layer was re-extracted with petrol/ethyl acetate (7:2, 2×10 mL). The combined organic layers were dried and evaporated. The crude product was crystallized from petrol/ethyl acetate (10:1, 15 mL) and left for 30 min at room temperature then at 0 °C for 15 min to give white crystals of the *title* compound **38** (22 mg, 72%), mp: 71–73 °C [Found $(M+Na)^+$: 1204.1912, $C_{80}H_{156}NaO_4$ requires: 1204.1896], $[\alpha]_D^{20}$ −5.5 (*c* 0.74, $CHCl_3$), δ_H (500 MHz, $CDCl_3$): 5.33 (1H, td, *J* 6.3, 15.2 Hz), 5.24 (1H, dd, *J* 7.6, 15.2 Hz), 3.74–3.70 (1H, m), 2.73 (1H, dt, *J* 2.2, 5.3 Hz), 2.49–2.45 (1H, m), 2.43 (1H, dd, *J* 2.2, 7.3 Hz), 2.11–2.01 (2H, m), 1.96 (2H, q, *J* 6.7 Hz), 1.78–1.06 (134H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.3 Hz), 0.94 (3H, d, *J* 6.7 Hz), 0.89 (6H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 178.7, 136.5, 128.4, 72.1, 64.0, 59.0, 50.7, 37.2, 36.7, 36.0, 35.5, 33.8, 32.6, 32.2, 31.9, 29.9, 29.8, 29.7, 29.6, 29.53, 29.5, 29.4, 29.36, 29.1, 27.3, 27.2, 26.1, 25.7, 22.7, 21.0, 17.3, 14.1; ν_{max}: 3368, 2922, 2851, 1686, 1463, 1048 cm^{-1}.

4.1.22. (2S,3S)-2-(11-Bromoundecyl)-3-((R)-octadecan-2-yl)oxirane ***41***. Lithium bis(trimethylsilyl)amide (5.23 mL, 5.54 mmol, 1.06 M) was added dropwise to a stirred solution of aldehyde **18** (1.0 g, 3.0 mmol) and sulfone **40** (1.58 g, 3.69 mmol) in dry tetrahydrofuran (36 mL) under nitrogen at −10 °C. The mixture was allowed to reach room temperature and stirred for 1 h, then worked up and purified as before to give (2*S*,3*S*)-2-((*E*/*Z*)-11-bromoundec-1-enyl)-3-((*R*)-octadec-an-2-yl)oxirane (1.03 g, 63%). Hydrogenation was carried out with dipotassium azodicarboxylate (2.50 g, 12.9 mmol) as before; chromatography eluting with petrol/ethyl acetate (20:1) gave a white solid, the *title* compound **41** (1.0 g, 96%), mp: 44–46 °C [Found $(M+Na)^+$: 551.3796, $C_{31}H_{61}Br^{79}NaO$ requires: 551.3798], $[\alpha]_D^{24}$ −8.1 (*c* 1.05, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.40 (2H, t, *J* 7 Hz), 2.71 (1H, dt, *J* 2.2, 5.4 Hz), 2.41 (1H, dd, *J* 1.9, 7 Hz), 1.88–1.82 (3H, m), 1.54–1.24 (48H, br m, including br s at 1.26), 0.99 (3H, d, *J* 6.3 Hz), 0.88 (3H, t, *J* 7 Hz); δ_C (125 MHz, $CDCl_3$): 63.8, 58.8, 36.0, 33.9, 33.8, 32.8, 32.2, 31.9, 29.9, 29.7, 29.65, 29.63, 29.61, 26.0, 29.52, 29.5, 29.4, 29.3, 28.7, 28.2, 27.2, 26.1, 22.7, 17.2, 14.2, 14.1; ν_{max}: 2924, 2853, 1465, 1376 cm^{-1}.

4.1.23. 5-(11-((2S,3S)-3-((R)-Octadecan-2-yl)oxiran-2-yl)undecyl sulfonyl)-1-phenyl-1H-tetrazole ***42***.

(i) Bromide **41** (1.0 g, 1.9 mmol) was added with vigorous stirring to 1-phenyl-1*H*-tetrazole-5-thiol (0.37 g, 2.1 mmol) and anhydrous potassium carbonate (0.52 g, 3.8 mmol) in acetone (35 mL). The mixture was heated under reflux for 2.5 h, then worked up and purified as before to give a white solid, 5-(11-((2*S*,3*S*)-3-((*R*)-octadecan-2-yl)oxiran-2-yl)undecyl-thio)-1-phenyl-1*H*-tetrazole (0.84 g, 71%), mp: 39–40 °C [Found $(M+H)^+$: 627.5033, $C_{38}H_{67}N_4OS$ requires: 627.5035], $[\alpha]_D^{21}$ −4.8 (*c* 0.99, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.60–7.53 (5H, m), 3.39 (2H, t, *J* 7.3 Hz), 2.71 (1H, dt, *J* 2.2, 5.7 Hz), 2.41(1H, dd, *J* 2.2, 7.3 Hz), 1.82 (1H, pent., *J* 7.3 Hz), 1.54–1.22 (50H, m, including br s at 1.26), 0.99 (3H, d, *J* 6.3 Hz), 0.88 (3H, t, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 154.5, 133.8, 130.0, 129.7, 123.9, 63.8, 58.8, 36.0, 33.8, 33.4, 32.2, 31.9, 29.9, 29.7, 29.65, 29.63, 29.6, 29.52, 29.5, 29.4, 29.3, 29.1, 29.0, 28.6, 27.2, 26.1, 22.7, 17.2, 14.1; ν_{max}: 2923, 2852, 1500, 1466, 1385, 1243, 1073 cm^{-1}.

(ii) Ammonium molybdate (VI) tetrahydrate (0.70 g, 0.57 mmol) in ice cold H_2O_2 (35% w/w, 3 mL) was added to a stirred solution of the above tetrazole (0.79 g, 1.25 mmol) in THF (10 mL) and IMS (25 mL) at 12 °C and stirred at rt for 2 h. Further ammonium molybdate (VI) tetrahydrate (0.3 g, 0.24 mmol) in ice cold H_2O_2 (35% w/w, 2 mL) was added and the mixture was stirred at rt 18 h, then worked up and purified as before to give a white solid, the *title* compound **42** (0.70 g, 84%), mp: 42–44 °C [Found $(M+H)^+$: 659.4907, $C_{38}H_{67}N_4O_3S$ requires: 659.4928], $[\alpha]_D^{20}$ −14.2 (*c* 0.79, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.69 (2H, m), 7.63–7.58 (3H, m), 3.73 (2H, t, *J* 7.9 Hz), 2.71 (1H, dt, *J* 2.2, 5.7 Hz), 2.41 (1H, dd, *J* 2.2, 7.0 Hz), 1.99–1.92 (2H, m), 1.58–1.22 (49H, m, including br s at 1.26), 1.0 (3H, d, *J* 6.3 Hz), 0.88 (3H, t, *J* 6.7 Hz); δ_C (125 MHz, $CDCl_3$): 153.6, 133.1, 131.4, 129.7, 125.1, 63.8, 58.8, 56.1, 36.0, 33.8, 32.2, 31.9, 29.9, 29.7, 29.63, 29.6, 29.5, 29.45, 29.43, 29.4, 29.3, 29.2, 28.9, 28.1, 27.2, 26.1, 22.7, 21.9, 17.2, 14.1; ν_{max}: 2923, 2853, 1463, 1342, 1152 cm^1.

4.1.24. ((1S,2R)-2-(Tetrahydro-2H-pyran-2-yloxy)methyl)-cyclopropyl butyrate ***45***. 3,4-Dihydro-2*H*-pyran (7.81 g, 92.9 mmol) and pyridinium-*p*-toluene sulfonate (0.58 g, 2.32 mmol) were added to a stirred solution of ((1*S*,2*R*)-2-(hydroxymethyl)cyclopropyl) methyl butyrate[42] (8.0 g, 46 mmol) in dry CH_2Cl_2 (150 mL) under nitrogen at rt. The reaction was stirred for 3 h and worked up with satd aq $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried and evaporated; column chromatography on silica gel eluting with petrol/ethyl acetate (10:1) to give a colourless oil, the *title* compound **45** as a mixture of diastereoisomers (10.0 g, 84%) [Found $(M+Na)^+$: 279.1594, $C_{14}H_{24}NaO_4$ requires: 279.1567], $[\alpha]_D^{20}$ +2.01 (*c* 1.19, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.61 (1H, t, *J* 3.8 Hz), 4.53 (1H, t, *J* 4.1 Hz), 4.16 (1H, td, *J* 2.2, 3.5 Hz), 4.14 (1H, dd, *J* 2.2, 7.6 Hz), 4.04–3.97 (2H, m), 3.85–3.75 (3H, m), 3.63–3.6 (1H, m), 3.51–3.43 (3H, m), 3.32 (1H, br dd, *J* 7.6,

10.8 Hz), 2.26 (2H, t, *J* 7.3 Hz), 2.25 (2H, t, *J* 7.6 Hz), 1.82–1.77 (2H, m), 1.70–1.46 (14H, m), 1.28–1.22 (4H, m), 0.91 (6H, t, *J* 7.3 Hz), 0.85–0.79 (2H, m), 0.28 (1H, q, *J* 5.4 Hz), 0.25 (1H, q, *J* 5.4 Hz); δ_C (125 MHz, $CDCl_3$): 173.6, 173.6, 98.7, 98.21, 94.5, 67.1, 67.0, 64.5, 64.45, 62.2, 61.9, 36.1, 30.6, 30.57, 30.5, 25.4, 25.3, 19.6, 19.5, 19.3, 18.3, 15.6, 15.3, 14.4, 14.2, 13.5, 8.5, 8.3; ν_{max}: 2942, 2874, 1735, 1458, 1374, 1259, 1183, 1026 cm^{-1}.

4.1.25. ((1S,2R)-2-((Tetrahydro-2H-pyran-2-yloxy)methyl)-cyclopropyl) methanol ***46***. ((1*S*,2*R*)-2-((Tetrahydro-2*H*-pyran-2-yloxy) methyl)cyclopropyl butyrate (10.0 g, 39 mmol) in tetrahydrofuran (50 mL) was added dropwise over 15 min to a suspension of lithium aluminium hydride (2.28 g, 58.5 mmol) in tetrahydrofuran (200 mL) at room temperature. The mixture was heated under reflux for 1 h, then worked up and purified as before to give a colourless oil, the title compound **46** as a mixture of diastereoisomers (6.7 g, 92%) [Found $(M+Na)^+$: 209.1, $C_{10}H_{18}NaO_3$ requires: 209.1],[49] $[\alpha]_D^{20}$ +17.7 (*c* 1.19, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.64–2.62 (2H, m), 4.18 (1H, dd, *J* 5.7, 11.1 Hz), 3.93–3.85 (4H, m), 3.82–3.78 (1H, m), 3.53–3.46 (2H, m), 3.37 (1H, t, *J* 11 Hz), 3.24 (1H, dd, *J* 10.4, 12.0 Hz), 3.19 (1H, dd, *J* 10.7, 12.0 Hz), 3.09 (1H, t, *J* 10.8 Hz), 2.8 (1H, br s), 1.82–1.75 (1H, m), 1.74–1.62 (3H, m), 1.6–1.46 (9H, m), 1.37–1.29 (2H, m), 1.28–1.20 (2H, m), 0.8–0.75 (2H, m), 0.19–0.14 (2H, m); δ_C (125 MHz, $CDCl_3$): 98.8, 98.2, 67.9, 67.7, 62.9, 62.6, 62.5, 62.1, 30.5, 30.4, 25.2, 25.1, 19.6, 19.2, 18.4, 18.37, 14.9, 14.5, 8.1, 8.05; ν_{max}: 3435, 2924, 2854, 1456, 1377, 1118, 1021 cm^{-1}.

4.1.26. (1S,2R)-2-((Tetrahydro-2H-pyran-2-yloxy)methyl)cyclopropanecarbaldehyde ***47***. (1*S*,2*R*)-2-((Tetrahydro-2*H*-pyran-2-yloxy)methyl)cyclopropyl)methanol (6.48 g, 34.79 mmol) in dichloromethane (15 mL) was added to a stirred suspension of pyridinium chlorochromate (18.7 g, 87.0 mmol) in dichloromethane (250 mL) at room temperature. The mixture was stirred vigorously for 3 h then worked up as before and purified by chromatography on silica gel eluting with petrol/ethyl acetate (1:1) to give a colourless oil, the *title* compound **47** as a mixture of diastereoisomers (3.5 g, 54%), $[\alpha]_D^{18}$ +19.3 (*c* 1.15, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.4 (1H, t, *J* 4.7 Hz), 9.38 (1H, t, *J* 5.1 Hz), 4.59–4.58 (1H, m), 4.45–4.43 (1H, m), 4.11 (1H, dd, *J* 2.2, 5.7 Hz), 3.83–3.76 (1H, m), 3.75–3.72 (1H, m), 3.71–3.56 (1H, m), 3.48–3.42 (2H, m), 3.35–3.30 (1H, m), 2.01–1.91 (2H, m), 1.83–1.68 (3H, m), 1.65–1.60 (2H, m), 1.53–1.46 (8H, m), 1.30–1.24 (2H, m),1.23–1.17 (2H, m), 0.54–0.49 (1H, m), 0.17–0.15 (1H, m); δ_C (125 MHz, $CDCl_3$): 200.2, 200.1, 98.7, 98.1, 65.2, 65.1, 62.2, 61.7, 30.4, 30.3, 26.8, 26.78, 25.2, 23.5, 23.0, 19.4, 19.0, 13.9, 12.0, 11.96; ν_{max}: 2944, 2871, 1704, 1371, 1201, 1172, 1120, 1061 cm^{-1}.

4.1.27. ((1R,2S)-2-(16-(tert-Butyldiphenylsilyloxy)hexadecyl)cyclopropyl)methanol ***50***. (a) Lithium bis(trimethylsilyl)amide (18.0 mL, 28.7 mmol, 1.06 M) was added dropwise with stirring to aldehyde **47** (2.94 g, 15.95 mmol) and ester **26** (8.88 g, 20.7 mmol) in dry THF (100 mL) under nitrogen at −10 °C. The mixture was allowed to reach rt and stirred for 1.5 h, then worked up as before and purified by chromatography eluting with petrol/ethyl acetate (7:1) to give a colourless oil, methyl (*E*/*Z*)-16-((1*R*,2*R*)-2-((tetrahydro-2*H*-pyran-2-yloxy)methyl)cyclopropyl)hexadec-15-enoate (6.0 g, 89%), which was used for the next step without further analysis; (b) the above ester (6 g, 14.19 mmol) in tetrahydrofuran (25 mL) was added dropwise over 15 min to a suspension of lithium aluminium hydride (0.810 g, 21.3 mmol) in tetrahydrofuran (150 mL) at room temperature. The mixture was heated under reflux for 1 h, then worked up as before and purified by chromatography on silica gel eluting with petrol/ethyl acetate (2:1) to give a colourless oil, (*E*/*Z*)-16-((1*R*,2*R*)-2-((tetrahydro-2*H*-pyran-2-yloxy)-methyl)cyclopropyl) hexadec-15-en-1-ol **48** (4.5 g, 80%), which was used for the next step without further analysis; (c) Triethylamine (1.38 mL, 13.7 mmol) was added dropwise at 0 °C to a stirred solution of **48** (4.50 g, 11.4 mmol) in dry dichloromethane (50 mL) under nitrogen. After stirring for 10 min, *tert*-butyl diphenylchlorosilane (3.44 g, 12.5 mmol) was added followed by the addition of 4-dimethylaminopyridine (29 mg). The mixture was then stirred for 5 h at rt followed by quenching with water (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic layers were dried and concentrated to give the crude product; chromatography eluting with petrol/ethyl acetate (5:1) gave a colourless oil (6.9 g, 95%), which was used for next step without further analysis; (d) A solution of pyridinium-*p*-toluene sulfonate (1.36 g, 5.42 mmol) in methanol (10 mL) was added to a stirred solution of the above silane (6.9 g, 10.9 mmol) in THF (40 mL) and stirred at 50 °C overnight. Satd aq $NaHCO_3$ (10 mL) and water (25 mL) were added and extracted with ethyl acetate (3×40 mL). The combined organic layers were dried and the solvent was evaporated. Column chromatography eluting with petrol/ethyl acetate (6:1) gave a colourless oil, ((1*R*,2*R*)-2-((*E*/*Z*)-16-(*tert*-butyldiphenylsilyloxy)hexadec-1-enyl)cyclopropyl)methanol **49** (4.9 g, 82%); (e) Hydrogenation was carried out with dipotassium azodicarboxylate as before and the product was purified by column chromatography eluting with petrol/ethyl acetate (2:1) to give a colourless oil of the *title* compound **50** (4.8 g, 98%) [Found $(M+Na)^+$: 573.4099, $C_{36}H_{58}NaO_2Si$ requires: 573.4098], $[\alpha]_D^{22}$ +7.47 (*c* 1.07, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.70–7.68 (4H, m), 7.45–7.37 (6H, m), 3.68–3.64 (3H, including t at δ 3.67 (*J* 6.3 Hz)), 3.59 (1H, dd, *J* 7.9, 11.0 Hz), 1.57 (2H, pent, *J* 7 Hz), 1.49–1.23 (29H, m), 1.12–1.10 (1H, m), 1.06 (9H, s), 0.92–0.84 (1H, m), 0.71 (1H, dt, *J* 4.5, 8.2 Hz), −0.019 (1H, br q, *J* 5.4 Hz); δ_C (125 MHz, $CDCl_3$): 135.5, 134.2, 129.4, 127.5, 64.0, 63.3, 32.6, 30.2, 29.7, 29.65, 29.63, 29.6, 29.55, 29.4, 28.5, 26.8, 25.7, 19.2, 18.1, 16.1, 9.5; ν_{max}: 3368, 3072, 2924, 2853, 1746, 1593, 1463, 1428, 1111, 1030 cm^{-1}.

4.1.28. (1R,2S)-2-(16-(tert-Butyldiphenylsilyloxy)hexadecyl)-cyclopropanecarbaldehyde ***51***. ((1*R*,2*S*)-2-(16-(*tert*-Butyldiphenylsilyloxy)hexadecyl)cyclopropyl)methanol (1.2 g, 2.2 mmol) in dichloromethane (15 mL) was added to a stirred suspension of pyridinium chlorochromate (1.17 g, 5.44 mmol) in dichloromethane (30 mL) at room temperature.[48] The mixture was stirred vigorously for 3 h then worked up as before; chromatography on silica eluting with petrol/ethyl acetate (1:1) gave a colourless oil, the *title* compound **51** (1.18 g, 98%), $[\alpha]_D^{23}$ +48.6 (*c* 1.11, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.35 (1H, d, *J* 5.7 Hz), 7.69–7.67 (4H, m), 7.44–7.36 (6H, m), 3.66 (2H, t, *J* 6.6 Hz), 1.89–1.84 (1H, m), 1.63–1.24 (33H, m, including br s at 1.26), 1.05 (9H, s); δ_C (125 MHz, $CDCl_3$): 201.8, 135.6, 134.2, 129.4, 127.5, 64.0, 32.6, 30.0, 29.7, 29.63, 29.61, 29.5, 29.4, 29.2, 28.2, 27.8, 26.9, 25.8, 24.8, 19.2, 14.7; ν_{max}: 3072, 2925, 2854, 1704, 1463, 1428, 1111 cm^{-1}.

4.1.29. tert-Butyl-(16-((1S,2R)-2-(12-((2S,3S)-3-((R)-octadecan-2-yl)-oxiran-2-yl)dodecyl)cyclopropyl)hexadecyloxy)diphenylsilane ***52***. Lithium bis(trimethylsilyl)amide (1.54 g, 1.63 mmol, 1.06 M) was added dropwise with stirring to aldehyde **51** (0.50 g, 0.91 mmol) and sulfone **42** (0.72 g, 1.09 mmol) in dry THF (30 mL) under nitrogen at −10 °C. The mixture was allowed to reach rt and stirred for 1.5 h, then quenched with NH_4Cl (5 mL) and petrol/ethyl acetate (1:1, 20 mL) at 0 °C. The organic layer was separated and the aqueous layer was re-extracted with petrol/ethyl acetate (1:1, 2×20 mL). The combined organic layers were dried and the solvent was evaporated. Column chromatography eluting with petrol/ethyl acetate (20:1) to give a colourless oil, *tert*-butyl-[16-((1*S*,2*R*)-2-{(*E*/*Z*)-12-[(2*S*,3*S*)-3-((*R*)-1-methylheptadecyl)oxiranyl]dodec-1-enyl} cyclopropyl)hexadecyloxy]diphenylsilane (0.8 g, 89%). Hydrogenation was carried out with potassium azodicarboxylate as before and

the product was purified by column chromatography eluting with petrol/ethyl acetate (20:1) to give a white semi solid, the *title* compound **52** (0.64 g, 80%) [Found $(M+Na)^+$: 1005.8743, $C_{67}H_{118}NaO_2Si$ requires: 1005.8793], $[\alpha]_D^{20}$ −4.9 (*c* 0.85, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.68 (4H, dd, *J* 1.3, 7.9 Hz), 7.43–7.36 (6H, m), 3.65 (2H, t, *J* 6.6 Hz), 2.72 (1H, dt, *J* 2.2, 5.7 Hz), 2.41(1H, dd, *J* 1.9, 6.9 Hz), 1.60–1.22 (85H, br m, including br s at 1.25), 1.05 (9H, s), 1.0 (3H, d, *J* 6.0 Hz), 0.89 (3H, t, *J* 6.7 Hz), 0.67–0.64 (2H, m), 0.56 (1H, br dt, *J* 4.1, 8.2 Hz), −0.32 (1H, q, *J* 5.1 Hz); δ_C (125 MHz, $CDCl_3$):135.6, 134.2, 129.4, 127.5, 64.0, 63.9, 58.9, 36.0, 33.8, 32.6, 32.3, 31.9, 30.2, 29.9, 29.74, 29.7, 29.63, 29.6, 29.58, 29.5, 29.4, 29.36, 28.7, 27.2, 26.9, 26.1, 25.8, 22.7, 19.2, 17.3, 15.8, 14.1, 10.9; ν_{max}: 3072, 2924, 2853, 1464, 1111 cm^{-1}.

*4.1.30. 16-((1S,2R)-2-{12-[(2S,3S)-3-((R)-1-Methylheptadecyl)oxiranyl]dodecyl}cyclopropyl)hexadecanal **53**.*

(i) Tetra-*n*-butyl ammonium fluoride (0.97 mL, 0.97 mmol, 1 M in THF) was added to a stirred solution of silane **52** (0.64 g, 0.65 mmol) in dry THF (30 mL) at 0 °C under nitrogen. The mixture was allowed to reach rt and stirred overnight, then cooled to 5 °C and quenched with satd aq NH_4Cl (5 mL) and the product extracted with ethyl acetate (3×50 mL), then washed with brine (20 mL), dried over $MgSO_4$ and the solvent was evaporated. Column chromatography eluting with petrol/ethyl acetate (6:1) gave a white solid, 16-((1*S*,2*R*)-2-{12-[(2*S*,3*S*)-3-((*R*)-1-methylheptadecyl)oxiranyl]dodecyl}-cyclopropyl)-hexadecan-1-ol (0.44 g, 91%), mp: 60–63 °C [Found $(M+H)^+$: 745.7781, $C_{51}H_{101}O_2$ requires: 745.7796], $[\alpha]_D^{25}$ −6.6 (*c* 1.07, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.64 (2H, t, *J* 6.6 Hz), 2.72 (1H, dt, *J* 2.2, 5.4 Hz), 2.41 (1H, dd, *J* 2.2, 7.3 Hz), 1.60–1.23 (86H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.0 Hz), 0.88 (3H, t, *J* 7.0 Hz), 0.69–0.64 (2H, m), 0.56 (1H, dt, *J* 4.1, 8.2 Hz), −0.32 (1H, q, *J* 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 63.9, 63.1, 58.9, 36.0, 33.8, 32.8, 32.3, 31.9, 30.2, 29.9, 29.72, 29.7, 29.63, 29.6, 29.58, 29.5, 29.4, 29.35, 28.7, 27.2, 26.5, 26.1, 25.7, 22.7, 17.3, 15.8, 14.1, 10.9; ν_{max}: 3418, 2925, 2854, 1464, 1112 cm^{-1}.

(ii) The above alcohol (0.44 g, 0.59 mmol) in dichloromethane (10 mL) was added to a stirred suspension of pyridinium chlorochromate (0.3 g, 1.47 mmol) in dichloromethane (30 mL) at rt. The mixture was stirred vigorously at rt for 2 h, then poured into petrol/ethyl acetate (10:1, 30 mL), filtered through a bed of silica and Celite then washed with petrol/ethyl acetate and the filtrate was evaporated to give a residue. Column chromatography on silica gel eluting with petrol/ethyl acetate (8:1) gave a white solid, the *title* compound **53** (0.33 g, 76%), mp: 49–51 °C, $[\alpha]_D^{21}$ −11 (*c* 0.7, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.77 (1H, t, *J* 1.6 Hz), 2.72 (1H, dt, *J* 1.9, 5.4 Hz), 2.44–2.40 (2H, m), 1.66–1.22 (84H, br m including br s at 1.26), 1.0 (3H, d, *J* 6 Hz), 0.88 (3H, t, *J* 6.6 Hz), 0.69–0.64 (2H, m), 0.56 (1H, dt, *J* 4.1, 8.2 Hz), −0.32 (1H, q, *J* 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 202.9, 63.9, 58.9, 43.9, 36.0, 33.8, 32.3, 31.9, 30.2, 29.9, 29.73, 29.7, 29.66, 29.63, 29.6, 29.5, 29.4, 29.35, 29.2, 28.7, 27.2, 26.5, 26.1, 22.7, 22.1, 17.3, 15.8, 14.1, 10.9; ν_{max}: 2922, 2851, 1731, 1463, 1372, 1231, 1115 cm^{-1}.

*4.1.31. Methyl (R)-2-[(R)-3-bromo-1-(tert-butyldimethylsilanyloxy) propyl]tetracosanoate **56**.* *N*-Bromosuccinimide (1.21 g, 6.83 mmol) was added in portions over 15 min to a stirred solution of methyl (*R*)-2-[(*R*)-1-(*tert*-butyldimethylsilanyloxy)-3-hydroxypropyl]-tetracosanoate (3.0 g, 5.3 mmol),[31] triphenylphosphine (1.72 g, 6.56 mmol) and sodium hydrogen carbonate (0.3 g) in dichloromethane (50 mL) at 0 °C. The mixture was stirred at rt for 1 h, then worked up and purified as before to give a pale yellow thick oil of the *title* compound **56** (2.0 g, 60%) [Found $(M+Na)^+$: 655.4085, $C_{34}H_{69}Br^{79}NaO_3Si$ requires: 655.4092], $[\alpha]_D^{22}$ +7.8 (*c* 1.06, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.10–4.07 (1H, m), 3.68 (3H, s), 3.46–3.42 (2H, m), 2.54 (1H, ddd, *J* 3.8, 5.7, 9.5 Hz), 2.09–2.02 (1H, m), 1.97 (1H, ddd, *J* 3.5, 7.9, 11.4 Hz), 1.67–1.22 (42H, br m, including br s at 1.26), 0.9–0.86 (12H, m, including s at 0.88 for the ^{t}Bu and a triplet at 0.89 with *J* 5.7 Hz), 0.11 (3H, s), 0.08 (3H, s); δ_C (125 MHz, $CDCl_3$): 174.1, 71.3, 51.6, 51.5, 36.8, 31.9, 29.7, 29.64, 29.61, 29.6, 29.55, 29.4, 29.35, 28.0, 26.5, 25.7, 22.7, 18.0, 14.1, 14.0, −4.6, −4.8; ν_{max}: 2924, 2854, 1741, 1463, 1254, 1072 cm^{-1}.

*4.1.32. Methyl (R)-2-[(R)-1-(tert-butyldimethylsilanyloxy)-3-(1-phenyl-1H-tetrazole-5-sulfonyl)propyl]tetracosanoate **57**.*

(i) (*R*)-2-((*R*)-3-Bromo-1-(*tert*-butyl-dimethylsilanyloxy)-propyl]-
tetracosanoic acid methyl ester (0.7 g, 1.1 mmol) was added with vigorous stirring to 1-phenyl-1*H*-tetrazole-5-thiol (0.21 g, 1.2 mmol) and anhydrous potassium carbonate (0.3 g, 2.2 mmol) in acetone (30 mL). The mixture was heated under reflux for 2.5 h, then worked up and purified as before to give a colourless oil, methyl (*R*)-2-[(*R*)-1-(*tert*-butyldimethyl-silanyloxy)-3-(1-phenyl-1*H*-tetrazole-5-ylsulfanylpropyl]tetracosanoate (0.76 g, 95%) [Found $(M+Na)^+$: 753.5174, $C_{41}H_{74}N_4NaO_3SSi$ requires: 753.5143], $[\alpha]_D^{22}$ −9.9 (*c* 0.82, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.61–7.51 (5H, m), 4.07 (1H, dt, *J* 4.1, 6.3 Hz), 3.66 (3H, s), 3.49–3.43 (1H, m), 3.40–3.34 (1H, m), 2.59 (1H, ddd, *J* 4.8, 7.0, 11.4 Hz), 2.14–2.07 (1H, m), 2.01–1.93 (1H, m), 1.59–1.21 (42H, br m, including br s at 1.25), 0.89–0.87 (12H, m, including s at 0.88 for ^{t}Bu and t at 0.87 with *J* 4.1 Hz), 0.07 (3H, s), 0.05 (3H, s); δ_C (125 MHz, $CDCl_3$)): 174.4, 154.2, 133.7, 130.1, 129.8, 123.8, 72.0, 51.5, 51.46, 33.1, 31.9, 29.7, 29.64, 29.63, 29.6, 29.5, 29.4, 28.6, 27.8, 27.1, 25.7, 22.7, 17.9, 14.1, −4.4, −4.9; ν_{max}: 2924, 2853, 1738, 1504, 1466, 1254, 1085 cm^{-1}.

(ii) Ammonium molybdate (VI) tetrahydrate (0.57 g, 0.46 mmol) in ice cold H_2O_2 (35% w/w, 1.5 mL) was added to a stirred solution of the above ester (0.75 g, 1.02 mmol) in IMS (15 mL) and THF (2 mL) at 12 °C and stirred at rt for 2 h. Further ammonium molybdate (VI) tetrahydrate (0.30 g, 0.22 mmol) in ice cold H_2O_2 (35% w/w, 1 mL) was added and the mixture was stirred at rt for 18 h, then worked up as before; column chromatography eluting with petrol/ethyl acetate (6:1) gave a white solid, the *title* compound **57** (0.71 g, 90%), mp: 65–67 °C [Found $(M+Na)^+$: 785.5025, $C_{41}H_{74}N_4NaO_5SSi$ requires: 785.5041], $[\alpha]_D^{20}$ −9.6 (*c* 0.82, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.70 (2H, m), 7.65–7.59 (3H, m), 4.16–4.12 (1H, m), 3.81–3.77 (2H, m), 3.68 (3H, s), 2.52 (1H, ddd, *J* 3.8, 7.6, 11.4 Hz), 2.23–2.07 (2H, m), 1.61–1.22 (42H, br m, including br s at 1.25), 0.89–087 (12H, m, including s at 0.88 for the ^{t}Bu and t at 0.87 with *J* 3.2 vHz), 0.10 (3H, s), 0.06 (3H, s); δ_C (125vMHz, $CDCl_3$): 174.1, 153.4, 133.0, 131.5, 129.7, 125.0, 123.8, 70.9, 51.7, 51.6, 51.3, 31.9, 29.7, 29.64, 29.6, 29.54, 29.5, 29.4, 29.35, 27.6, 27.4, 26.2, 25.7, 25.6, 22.7, 17.9, 14.1, −4.5, −5.1; ν_{max}: 2925, 2854, 1739, 1463, 1498, 1343, 1154, 1080 cm^{-1}.

*4.1.33. Methyl (R)-2-[(R)-1-(tert-butyldimethylsilanyloxy)-19-((1S, 2R)-2-{12-[(2S,3S)-3-((R)-1-methylheptadecyl)oxiranyl]dodecyl}cyclopropyl)nonadecyl]tetracosanoate **58**.* Lithium bis(trimethyl-silyl) amide (0.21 mL, 0.27 mmol, 1.06 M) was added dropwise with stirring to aldehyde **53** (0.12 g, 0.16 mmol) and sulfone **57** (0.14 g, 0.19 mmol) in dry tetrahydrofuran (10 mL) under nitrogen at −2 °C. The mixture was allowed to reach rt and stirred for 1.5 h, then worked up as before and purified by chromatography on silica gel eluting with petrol/ethyl acetate (20:1) to give methyl (*R*)-2-[(*E*/*Z*)-(*R*)-1-(*tert*-butyldimethylsilanyloxy)-19-((1*S*,2*R*)-2-{12-[(2*S*, 3*S*)-3-((*R*)-1-methylheptadecyl)oxiranyl]dodecyl}cyclopropyl)nonadec-3-enyl]tetracosanoate (0.14 g, 68%). Hydrogenation was carried out

with dipotassium azodicarboxylate as before; chromatography eluting with petrol/ethyl acetate (20:1) gave a semi solid, the *title* compound **58** (0.13 g, 92%) [Found $(M+Na)^+$: 1305.2684, $C_{85}H_{168}NaO_4Si$ requires: 1304.2604], $[\alpha]_D^{24}$ −6.95 (*c* 1.15, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 3.92–3.89 (1H, m), 3.66 (3H, s), 2.72 (1H, dt, *J* 2.2, 5.4 Hz), 2.53 (1H, ddd, *J* 3.8, 7.3, 11 Hz), 2.41 (1H, dd, *J* 2.2, 7.3 Hz), 1.70–1.22 (133H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.0 Hz), 0.88 (6H, t, *J* 7.0 Hz), 0.86 (9H, s), 0.66–0.64 (2H, m), 0.56 (1H, dt, *J* 4.1, 8.2 Hz), 0.05 (3H, s), 0.02 (3H, s), −0.32 (1H, q, *J* 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 175.1, 73.2, 63.8, 58.9, 51.6, 51.2, 36.1, 33.8, 33.7, 32.3, 31.9, 30.2, 29.9, 29.8, 29.7, 29.7, 29.6, 29.5, 29.44, 29.4, 28.7, 27.8, 27.5, 27.2, 26.1, 25.8, 23.7, 22.7, 22.6, 18.0, 17.3, 15.8, 14.1, 10.9, −4.4, −4.9; ν_{max}: 2924, 2853, 1741, 1464, 1377, 1258, 1170 cm^{-1}.

*4.1.34. (R)-2-[(R)-Hydroxy-19-((1S,2R)-2-{12-[(2S,3S)-3-((R)-1-methylheptadecyl)oxiranyl]dodecyl}cyclopropyl)nonadecyl]tetracosanoic acid **59**.*

(i) Ester **58** (0.18 g, 0.14 mmol) was dissolved in dry THF (15 mL) in a dry poly-ethylene vial under nitrogen at rt and stirred. Pyridine (0.2 mL) and hydrogen fluoride-pyridine complex (1.6 mL) were added and the mixture was stirred for 17 h at 40 °C, then worked up as before and purified by chromatography eluting with petrol/ethyl acetate (9:1) to give a white solid, methyl (*R*)-2-[(*R*)-1-hydroxy-19-((1*S*,2*R*)-2-{12-[(2*S*,3*S*)-3-((*R*)-1-methylheptadecyl)oxiranyl]dodecyl}cyclopropyl)nonadecyl]tetracosanoate (90 mg, 56%), mp: 47–49 °C [Found $(M+Na)^+$: 1190.1755, $C_{79}H_{154}NaO_4$ requires: 1190.1739], $[\alpha]_D^{21}$ −2.0 (*c* 0.54, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.71 (3H, s), 3.67–3.65 (1H, m), 2.72 (1H, dt, *J* 2.2, 5.4 Hz), 2.47–2.40 (2H, m, including dd at 2.41, *J* 1.9, 7.0 Hz), 1.74–1.22 (134H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.3 Hz), 0.88 (6H, t, *J* 7.0 Hz), 0.69–0.64 (2H, m), 0.56 (1H, dt, *J* 4.1, 7.9 Hz), −0.32 (1H, q, *J* 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 176.2, 72.3, 63.9, 58.7, 51.5, 50.9, 36.0, 35.7, 33.8, 32.3, 31.9, 30.2, 29.9, 29.7, 29.7, 29.63, 29.61, 29.6, 29.53, 29.5, 29.42, 29.4, 28.7, 27.4, 27.2, 26.1, 25.7, 22.7, 17.3, 15.8, 14.1, 10.9; ν_{max}: 3472, 2924, 2853, 1727, 1464, 1377, 1166 cm^{-1}.

(ii) Lithium hydroxide monohydrate (43 mg, 1.02 mmol) was added to a stirred solution of the above ester (80 mg, 0.068 mmol) in THF (4 mL), methanol (0.5 mL) and water (0.7 mL) at rt. The mixture was stirred at 45 °C overnight, then cooled to rt and a mixture of petrol/ethyl acetate (7:2, 10 mL) was added. The mixture was acidified to pH 1 with potassium hydrogen sulfate and worked up as before. Column chromatography eluting with petrol/ethyl acetate (7:2) gave a white solid, the *title* compound **59** (60 mg, 76%), mp: 60–63 °C [Found $(M+Na)^+$: 1176.1544, $C_{78}H_{152}NaO_4$ requires: 1176.1583], $[\alpha]_D^{24}$ −8.4 (*c* 0.9, $CHCl_3$), which showed δ_H: 3.73–3.70 (1H, m), 2.73 (1H, dt, *J* 2.2, 5.7 Hz), 2.48–2.44 (1H, m), 2.43 (1H, dd, *J* 2.2, 7.3 Hz), 1.77–1.70 (1H, m), 1.63–1.22 (134H, br m, including br s at 1.26), 1.0 (3H, d, *J* 6.0 Hz), 0.88 (6H, t, *J* 6.6 Hz), 0.69–0.65 (2H, m), 0.56 (1H, dt, *J* 4.1, 8.2 Hz), −0.32 (1H, q, *J* 5.1 Hz); δ_C: 179.0, 72.1, 64.0, 59.0, 50.7, 36.0, 35.5, 33.8, 32.2, 31.9, 30.2, 29.9, 29.7, 29.6, 29.5, 29.42, 29.4, 28.7, 27.3, 27.2, 26.1, 25.7, 22.7, 17.3, 15.8, 14.1, 10.9; ν_{max}: 3375, 2917, 2849, 1683, 1465, 1381, 1266, 1070 cm^{-1}.

Acknowledgements

We thank the Government of Iraq for the award of a grant to DK.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.089.

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