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The synthesis of single enantiomers of meromycolic acids from mycobacterial wax esters

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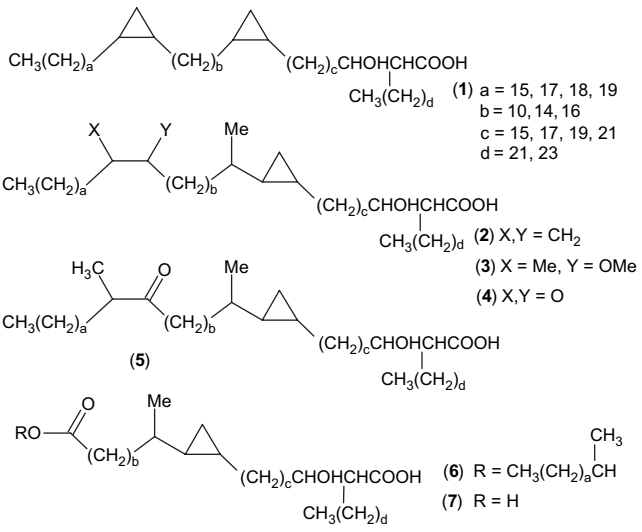
Abstract—Three stereoisomers of a wax ester meromycolate have been prepared starting from mannitol. A detailed comparison of their NMR spectra with those reported for a homologous series of natural wax esters allows the relative configurations of the α-methyl group and adjacent *trans*-cyclopropane to be determined.

1. Introduction

Mycobacterial cell walls show unusually low permeability, a factor which contributes to their resistance to therapeutic agents, apparently due to an exceptionally thick monolayer formed by the packing of esters of C_{60}–C_{90} fatty acids.[1] These 'mycolic acids', exemplified by structures **1**–**5**, contain various structural features including *cis*-cyclopropanes **1**,[2] α-methyl-*trans*-cyclopropanes, α-methyl-β-methoxy and α-methyl-β-keto,[3–6] *cis*-alkene, α-methyl-*trans*-alkene and α-methyl-*trans*-epoxy fragments, e.g., **4**.[7] Each contains a common β-hydroxy acid group[8,9] and they are generally present as mixtures of various chain lengths. Although the hydroxy acid grouping is known to be of *R*,*R*-configuration for a number of bacteria,[10] little is known about the absolute stereochemistries of the other groups. There is some evidence that the 1-methyl-2-methoxy unit at the distal position from the hydroxy acid in mycolic acids **3** is *S*,*S*,[10,6] while other reports identify a *R*-stereochemistry for the three stereocentres of the α-methyl-*trans*-epoxy unit in **4**.[7]

Over 60 years ago, Anderson, in an epic series of papers, initiated studies on mycobacterial lipids and reported[11] that the isolation of two new optically active long-chain alcohols from the neutral fraction of the saponified waxes of the so-called 'timothy bacillus', later classified as *Mycobacterium phlei*.[1] These alcohols were identified as *d*-2-eicosanol [$[\alpha]_D$ +3.5] and *d*-2-octadecanol [$[\alpha]_D$ +5.7]. It was noted that the acidic fraction from these saponified waxes contained a high molecular weight component, tentatively identified as being dibasic.[11] A careful analysis[11a] of the firmly bound lipids from avian tubercle bacilli (*Mycobacterium avium*) again yielded long-chain alcohols, with *d*-2-eicosanol as main component. These lipid fractions also produced a long-chain diacid, recognized for the first time as a mycolic acid and given the title γ-mycolic acid [$[\alpha]_D$ +5.3].[11a] In parallel studies, similar alcohols and acids were characterized from an organism claimed to be the causative agent of leprosy.[11b] It is clear, however, that this bacterium was not the leprosy bacillus as *Mycobacterium leprae* has not been cultivated to date and the mycolic acid composition of *M. leprae* is distinct (Scheme 1).[11c]



Scheme 1.

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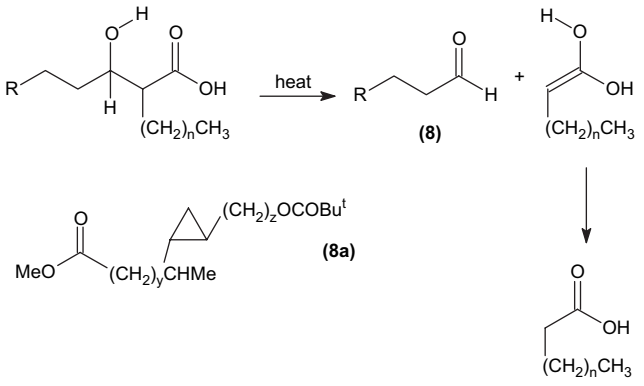
In more recent investigations of mycolic acid structure and distribution, compounds such as **6** or the corresponding diacids **7** were characterized from *Mycobacterium paratuberculosis*[12a] and *Mycobacterium gordonae*,[12b] as a constituent of trehalose mycolates of *M. phlei*,[13–17] including the identification of a trehalose monomycolate ester[13] and *Mycobacterium flavescens*.[17] They are known to be a characteristic component in the *M. avium–Mycobacterium intracellulare* group and other rapidly growing bacteria.[17,28] Their presence in *Mycobacterium smegmatis* has been implied,[19] although not confirmed by a later study.[20] Usually they have been analyzed as the corresponding α-methyl-alkanol and free acid after hydrolysis.[20,21] Some such wax esters do not appear to contain cyclopropanes, while in other cases the composition is not clear.[22–27] The analysis of the intact trehalose monomycolate derivatives by MALDI-TOF mass spectrometry shows ions due to C_{83}, C_{85} and C_{87} wax esters for *M. avium–M. intracellulare* (the italicized species being the major one), and C_{78}, C_{79}, C_{80}, C_{81}, C_{82} and C_{83} for *M. phlei* and *M. flavescens*.[17,18]

Much is now known about the enzymes controlling the biosynthesis of mycolic acids,[3,5,7,29] and a number of proposals have been made as to the relationship between routes to the different types, e.g., that the *cis*-cyclopropane unit, the α-methyl-*trans*-cyclopropane and the α-methyl-β-alkoxy unit are formed from a *Z*-alkene through a common intermediate.[30] A consequence of this would be that the three subunits should have a common absolute stereochemistry at the carbon bearing the methyl group and C-1 of the *cis*-cyclopropane. The number of carbons in the chains of wax esters closely matches with that of the corresponding keto-acids, and they have been shown to be related to them, apparently through a Baeyer–Villiger type process.[21,31,32]

A standard method for characterizing mycolic acids is thermolysis to fragment the hydroxy acid functionality to produce a 'meromycol-aldehyde' (**8**).[23] This can be oxidized to the corresponding 'meromycolic acid' and then protected as a derivative such as **8a** from **7** (Scheme 2).

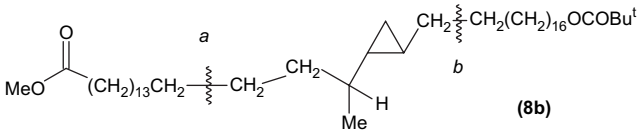


Scheme 2.

In this way, Anderson et al. were able to cleave the diacid ($[\alpha]_D$ in $CHCl_3$ +6.1) from the hydrolysis of timothy bacillus (*M. phlei*) wax ester to produce a mero-compound as a mixture ($[\alpha]_D$ in $CHCl_3$ +3.8).[33]

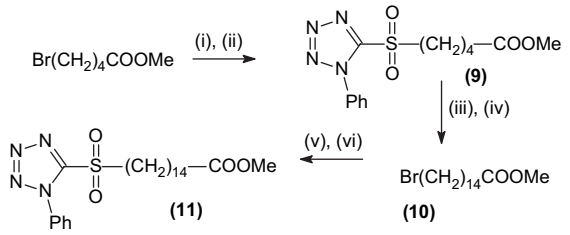
2. Results and discussion

The meromycolates derived from diacids **7** represent interesting synthetic targets because they contain only one group of chiral centres, those of the α-methyl-*trans*-cyclopropane, and may allow the overall chirality of this part of the mycolic acid system to be determined. We have already reported the synthesis of single enantiomers of one example of a di-*cis*-cyclopropane containing mycolic acid **1**,[34] of a corresponding meromycolate,[35] and of one enantiomer of the α-methyl-*trans*-cyclopropane unit present in **6** and **7**.[36] We now report the synthesis of three stereoisomers of the protected derivative **8b**, using a method that can be readily adapted to produce any appropriate chain length. In each case, the synthesis involves forming bonds *a* and *b* in Scheme 3 to a central chiral core derived from mannitol. This was achieved by the use of modified Kocienski–Julia reactions[37] to couple the fragments to produce an *E*/*Z* mixture of alkenes, followed by saturation of the alkene.



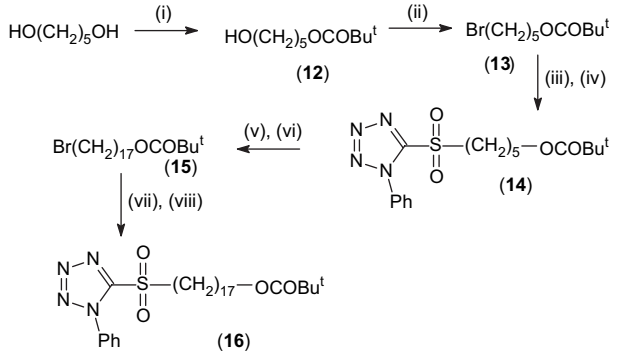
Scheme 3.

The key 15 carbon unit **11** for the left hand fragment was prepared from methyl 5-bromopentanoate as in Scheme 4.



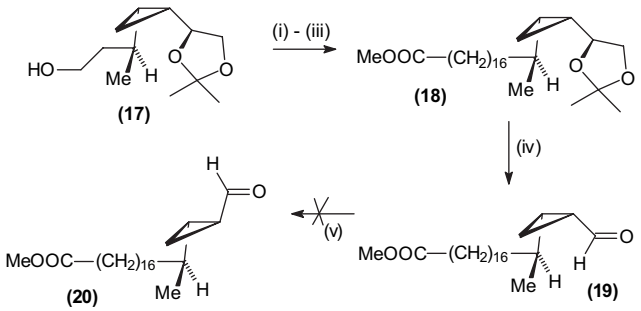
Scheme 4. (i) 1-Phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (92%); (ii) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (81%); (iii) LiHMDS, $Br(CH_2)_9CHO$ (80%); (iv) H_2, Pd/C (92%); (v) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (91%); (vi) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (91%).

In a similar way, the 17 carbon unit **16** for the right hand fragment was obtained from pentan-1,5-diol (Scheme 5).



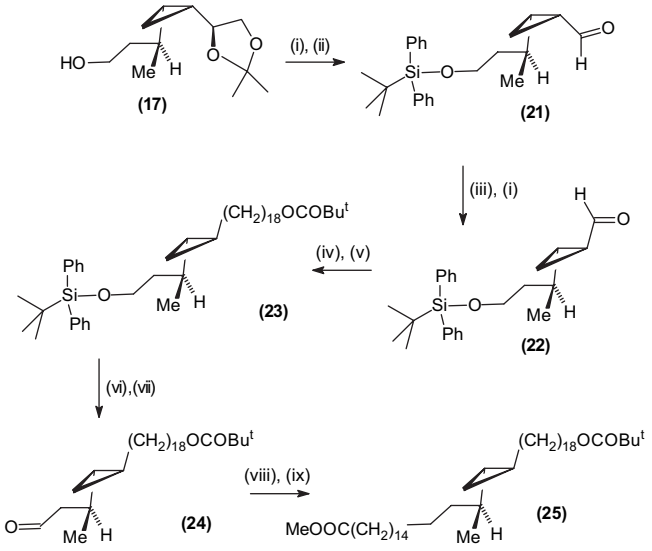
Scheme 5. (i) Pivaloyl chloride, pyridine (84%); (ii) *N*-bromosuccinimide, PPh_3 (92%); (iii) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (97%); (iv) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (99%); (v) $Br(CH_2)_{11}CHO$, LiHMDS (72%); (vi) H_2, Pd/C (88%); (vii) 1-phenyl-1*H*-tetrazol-5-thiol, K_2CO_3 (88%); (viii) H_2O_2, $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, IMS (98%).

In the first approach, it was hoped to create bond *a* in Scheme 3 first. The alcohol **17**, which we have reported earlier,[36] was oxidized to the corresponding aldehyde then treated with sulfone **11** and a base in a modified Kocienski–Julia reaction,[37] followed by saturation of the intermediate alkene to give ester **18**, introducing the acid chain adjacent to the methyl branch. Cleavage of the acetal gave the *cis*-aldehyde **19**, but this did not give the trans-isomer **20** on attempted epimerization with base (Scheme 6).



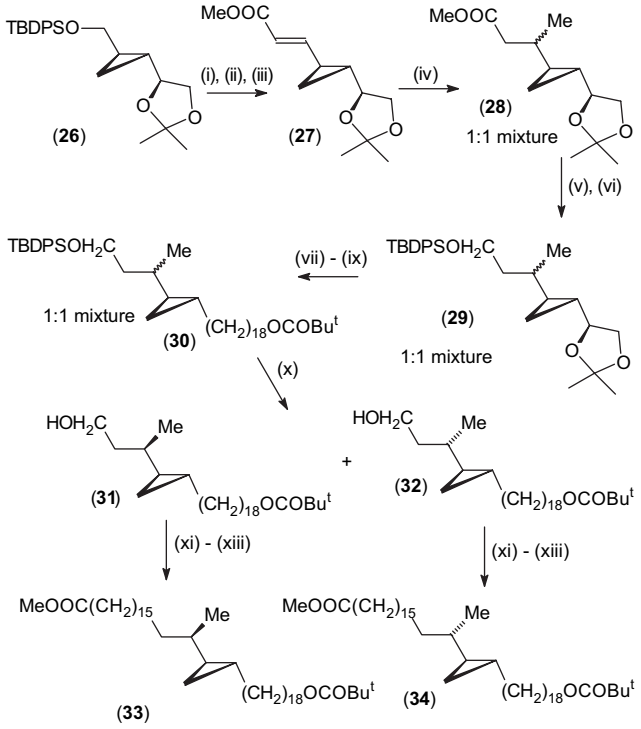
Scheme 6. (i) PCC (88%); (ii) LiHMDS, **11** (48%); (iii) KOOCNNCOOK, AcOH (62%); (iv) HIO_4 (80%); (v) NaOMe.

Given this failure, the other alkyl chain was instead introduced first to create bond *b* in Scheme 3. The alcohol **17** was protected as a silyl ether and then oxidized to *cis*-aldehyde **21**, following a route described earlier.[38,39] Epimerization with NaOMe in MeOH gave the *trans*-aldehyde **22**. Homologation with the sulfone **16** and base by a Julia–Kocienski reaction,[37] and subsequent saturation of the derived *E*/*Z*-alkene mixture using di-imide gave the ester **23** (Scheme 7).



Scheme 7. (i) Bu^tPh_2SiCl, Et_3N, CH_2Cl_2, DMAP (87%); (ii) HIO_4 (96%); (iii) NaOMe (followed by (i), overall 61%); (iv) LiHMDS, **16** (78%); (v) KOOCN=NCOOK, AcOH, MeOH (99.5%); (vi) Bu_4NF, THF (89%); (vii) PCC (83%); (viii) LiHMDS, **11** (55%); (ix) KOOCN=NCOOK, AcOH, MeOH (65%).

Removal of the silyl protecting group from **23**, followed by oxidation gave the aldehyde **24**. Reaction of the sulfone **11** (prepared from methyl 15-bromopentadecanoate) with the aldehyde **24**, again in a modified Julia reaction, led, after saturation of the *E*/*Z*-alkene mixture, to the diester **25**. The diester was converted into the corresponding ester alcohol by hydrolysis with KOH in methanol (95%) followed by re-esterification of the acid with diazomethane (84%). The enantiomer of **25** and **33** and one enantiomer of its diastereoisomer, **34** were prepared from compound **26**, again derived from mannitol (Scheme 8).[38,40]



Scheme 8. (i) Bu_4NF, THF (91%); (ii) PCC, CH_2Cl_2 (91%); (iii) $Ph_3P{=}CHCO_2Me$, toluene (79%); (iv) MeMgBr, CuBr, THF (70%); (v) $LiAlH_4$, THF (92%); (vi) Bu^tPh_2SiCl, imidizole, DMF (87%); (vii) HIO_4 (92%); (viii) LiHMDS, **16** (80%); (ix) KOOCN=NCOOK, AcOH, MeOH (80%); (x) Bu_4NF, THF (88%); (xi) PCC (89%); (xii) LiHMDS, **11** (65%); (xiii) KOOCN=NCOOK, AcOH, MeOH (80%); (xi) PCC (89, 90%) (for **31** and **32**, respectively); (xii) LiHMDS, **11** (65, 70%); (xiii) KOOCN=NCOOK, AcOH, MeOH (80, 80%).

In this case, the addition of methyl magnesium bromide to the alkene gave a ca. 1:1 mixture of the two epimers of acetal **28**, which could not be separated by column chromatography. This mixture was therefore reduced to the corresponding mixture of alcohols and protected as the silyl ethers **29**. Chain extension using sulfone **16** and base followed by saturation of the double bond, and then removal of the silyl ether protection gave a mixture of epimeric alcohols **31** and **32**, which, in this case, could be separated. The two alcohols were then separately chain extended to give **33** and **34** using the same method as described above for **25**.

The ^1H and ^{13}C NMR spectra of **25** and **33** were identical, as were their other spectra; however, they showed opposite specific rotations (+3.7 and −5.1, respectively) as did each of the single intermediates leading to them. The spectra for **34** were very similar to those for **25** and **33** but significant differences were seen in the high field regions in each case. Thus, although the cyclopropane regions of **25** and

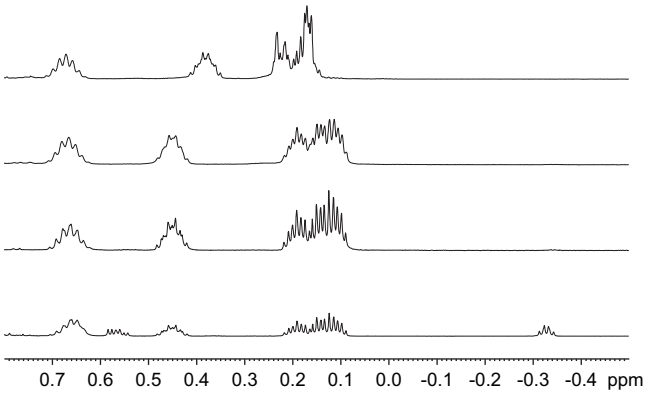
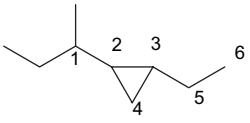


Figure 1. *Cyclopropane region of* ^1H *NMR* of (top to bottom) (i) **34**; (ii) **33**; (iii) **25**; (iv) a natural sample of the dimethyl ester of an ω-carboxy mycolic acid extracted from *M. avium*;[2] this sample contains mainly *trans*-cyclopropanes accompanied by some *cis*-cyclopropanes.

33 were visually identical to those reported for mixtures of wax ester meromycolates, and indeed to the same region in methoxymethylmycolates containing an α-methyl-*trans*-cyclopropane subunit, the same region of **34** was clearly different. Thus, Figure 1 shows the high field region of the ^{1}H NMR spectra of the three synthetic isomers, together with the same region for a natural wax ester—in which there is a mixture of *cis*- and α-methyl-*trans*-cyclopropanes. Moreover, there were small but significant differences in the carbon spectra between **25/33** and **34**; again the published shifts for either mycolic acids or wax esters containing the α-methyl-*trans*-cyclopropane unit were identical to the former. Thus, the relative stereochemistry of this unit is established. The close agreement between the rotation obtained for **25** and that reported by Anderson for a natural mero-wax acid suggests that the natural absolute stereochemistry is that of **25**, though the Anderson product was a mixture obtained well before modern spectroscopic techniques were available.[11] It will be interesting to compare his results with the rotations of mero-wax acids from other bacteria as these become available (Table 1).

Table 1. Selected ^{13}C NMR shifts for α-methyl-*trans*-cyclopropane fragment of natural wax esters and mycolic acids compared to **25/33** and **34**



1	2	3	4	Mycobacterium	Ref.
38.35	26.37	18.85	10.72	*M. tuberculosis*	41
38.13	26.14	18.62	10.50	*M. gordonae*	12b
38.1	18.6	26.1	10.50	*M. avium–M. intracellulare* complex	28
38.11	26.13	18.61	10.48	**25** *SRS*	
38.11	26.11	18.60	10.47	**33** *RSR*	
38.05	26.11	17.34	11.81	**34** *SSR*	

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, 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 Advance500 spectrometer; for carbon spectra, +=CH_2, −=CH, CH_3. $[\alpha]_D$ values were recorded in $CHCl_3$ on a POLAAR 2001 Optical Activity polarimeter. Mass spectra were recorded on a Bruker Microtof.

3.1.1. 5-(1-Phenyl-1*H*-tetrazol-5-sulfonyl)pentanoic acid methyl ester (9). Anhydrous potassium carbonate (50 g, 362 mmol) was added to a stirred solution of methyl 5-bromovalerate (37.1 g, 190 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (34 g, 190.8 mmol) in acetone (300 ml) at room temperature. After stirring vigorously at 40 °C for 3 h and at room temperature for 16 h, the precipitate was filtered off and washed with acetone, then the filtrate was evaporated to give a brown oil. This was diluted with dichloromethane (250 ml) and water (250 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 water (250 ml), dried and evaporated to give 5-(1-phenyl-1*H*-tetrazol-5-sulfanyl)pentanoic acid methyl ester as a brown oil (51 g, 92%) [Found $[M+H]^+$: 293.1070; $C_{13}H_{17}N_4O_2S$ requires: 293.1067], which showed δ_H (500 MHz, $CDCl_3$): 7.59–7.52 (5H, m), 3.65 (3H, s), 3.39 (2H, t, *J* 7.25 Hz), 2.36 (2H, t, *J* 7.25 Hz), 1.91–1.84 (2H, m), 1.8–1.74 (2H, m); δ_C (125 MHz, $CDCl_3$): 173.4, 154.2, 133.6, 130.1, 129.7, 51.5, 33.2, 32.8, 28.4, 23.7; ν_{max}: 2950, 1735, 1596, 1500 cm^{-1}. This was used for the next step without purification; to a vigorously stirred solution of the ester (27.8 g, 95 mmol) in tetrahydrofuran (250 ml) and industrial methylated spirits (250 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (18 g, 14.6 mmol) in ice cold 35% w/w hydrogen peroxide (50 ml). After three 30 min intervals a similar solution was added (total 72 g heptamolybdate in hydrogen peroxide (200 ml) was added). The mixture was stirred for 16 h at room temperature, diluted with water (2.5 l) and extracted with dichloromethane (2×400 ml). The combined organic layers were washed with water (1000 ml), dried and evaporated to give a thick yellow oil. Chromatography (1:1 petrol/ethyl acetate) gave 5-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentanoic acid methyl ester (**9**) (24.8 g, 81%) as a white solid, mp 61–63 °C [Found $[M+H]^+$: 325.0960; $C_{13}H_{17}N_4O_4S$ requires: 325.0965], which showed δ_H (500 MHz, $CDCl_3$): 7.68 (2H, br dd, *J* 1.25, 7.85 Hz), 7.63–7.57 (3H, m), 3.74 (2H, distorted t, *J* 7.85 Hz), 3.66 (3H, s), 2.38 (2H, t, *J* 7.25 Hz), 2.03–1.97 (2H, m), 1.83 (2H, br pent, *J* 7.55 Hz); δ_C (125 MHz, $CDCl_3$): 172.9, 153.3, 132.9, 131.4, 129.6, 125.0, 55.5, 51.7, 33.0, 23.2, 21.6; ν_{max}: 2954, 1734, 1498, 1342, 1153, 766 cm^{-1}.

3.1.2. 15-Bromopentadecanoic acid methyl ester (10). Lithium hexamethyldisilazide (49.2 ml, 49.2 mmol, 1 M

THF) was added dropwise with stirring at −10 °C to ester **9** (14.5 g, 44.68 mmol) and 10-bromodecanal (10 g, 42.55 mmol) in dry tetrahydrofuran (150 ml) under nitrogen. The reaction was exothermic and the temperature rose to −5 °C. The mixture was then stirred for 16 h at room temperature, when TLC showed no starting material, cooled to 0 °C, quenched with satd aq ammonium chloride (100 ml) and extracted with petrol/ether (1:1) (3×60 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil; chromatography (10:2 petrol/ether) gave 15-bromopenta-dec-5-enoic acid methyl ester as a pale yellow oil (11.33 g, 80%). Palladium on carbon (10%) (1 g) was added to a stirred solution of the ester (10.5 g, 31.53 mmol) in tetrahydrofuran (75 ml) and methanol (75 ml) under hydrogen. When no further hydrogen was absorbed, the products were filtered through Celite, which was washed with ethyl acetate. The filtrate was evaporated and the residue was purified by chromatography (5:2 petrol/ether) giving 15-bromopentadecanoic acid methyl ester (**10**) as a white solid (9.7 g, 92%), mp 38–39 °C (lit. 38–39 °C),[42] which showed δ_H (500 MHz, $CDCl_3$): 3.68 (3H, s), 3.42 (2H, t, *J* 7 Hz), 2.32 (2H, t, *J* 7.25 Hz), 1.86 (2H, br pent, *J* 7 Hz), 1.62 (2H, pent, *J* 7.25 Hz), 1.43 (2H, br pent, *J* 7 Hz), 1.28 (18H, br s); δ_C (125 MHz, $CDCl_3$): 174.4, 51.4, 34.1, 34.0, 32.8, 29.58, 29.55, 29.4, 29.2, 29.1, 28.8, 28.2, 24.9.

3.1.3. 15-(1-Phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic acid methyl ester (11). Anhydrous potassium carbonate (2.76 g, 20 mmol) was added to a stirred solution of ester **10** (2.75 g, 8.2 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (1.6 g, 9.0 mmol) in acetone (50 ml) at room temperature and stirred vigorously for 16 h. The precipitate was filtered off and washed with acetone, and the filtrate was evaporated to give a brown residue. This was diluted with dichloromethane (75 ml) and water (50 ml). The aqueous layer was re-extracted with dichloromethane (2×25 ml). The combined organic layers were washed with water (50 ml), dried and evaporated to give a yellow solid. Chromatography (5:1 petrol/ether) gave 15-(1-phenyl-1*H*-tetrazol-5-sulfanyl)pentadecanoic acid methyl ester (3.25 g, 91%) as a colourless thick oil, which showed δ_H (500 MHz, $CDCl_3$): 7.62 (5H, br s), 3.68 (3H, s), 3.41 (2H, t, *J* 7.6 Hz), 2.32 (2H, t, *J* 7.5 Hz), 1.83 (2H, pent, *J* 7.6 Hz), 1.64 (2H, br pent, *J* 7.6 Hz), 1.46 (2H, br pent, *J* 6.65 Hz), 1.27 (18H, br s); δ_C (125 MHz, $CDCl_3$): 174.3, 154.5, 133.8, 130.1, 129.8, 123.9, 51.4, 34.1, 33.4, 29.58, 29.55, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.6, 24.9; ν_{max}: 1732 cm^{-1}.

To a vigorously stirred solution of the above sulfide (3.2 g, 7.4 mmol) in tetrahydrofuran (45 ml) and industrial methylated spirits (45 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (4.2 g, 3.4 mmol) in ice cold 35% w/w hydrogen peroxide (13 ml) at 15 °C. After 1.5 h, a further ice cold solution of heptamolybdate (1.9 g) in hydrogen peroxide (5 ml) was added. The mixture was stirred for 16 h at room temperature then diluted with water (250 ml) and extracted with dichloromethane (2×50 ml). The combined organic layers were washed with water (100 ml), dried and evaporated to give a white solid; chromatography (1:1 petrol/ethyl acetate) gave 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic acid methyl ester (**11**) as a white solid (3.12 g, 91%), mp 78–80 °C [Found $[M+Na]^+$: 487.2343; $C_{23}H_{36}N_4O_4SNa$ requires: 487.2349], which showed δ_H (500 MHz, $CDCl_3$): 7.72 (2H, br dd, *J* 1.9, 8.2 Hz), 7.68–7.61 (3H, m), 3.75 (2H, distorted t, *J* 7.9 Hz), 3.68 (3H, s), 2.32 (2H, t, *J* 7.5 Hz), 1.97 (2H, br pent, *J* 7.55 Hz), 1.64 (2H, br pent, *J* 7.25 Hz), 1.5 (2H, pent, *J* 7.5 Hz), 1.27 (18H, br s); δ_C (125 MHz, $CDCl_3$): 174.3, 153.5, 133.1, 131.5, 129.7, 125.1, 56.0, 51.4, 34.1, 29.56, 29.54, 29.50, 29.44, 29.40, 29.20, 29.18, 29.1, 28.9, 28.2, 25.0, 22.0; ν_{max}: 2920, 1731, 1494, 1341, 1151 cm^{-1}.

3.1.4. 2,2-Dimethylpropionic acid 5-hydroxypentyl ester (12). Trimethylacetyl chloride (12 g, 95.39 mmol) was added to a stirred solution of 1,5-pentanediol (20 g, 192 mmol) and pyridine (10 g, 126 mmol) in dichloromethane (100 ml) at 10 °C, then allowed to reach room temperature and stirred for 16 h. A white precipitate was formed, and the mixture was diluted with dichloromethane (200 ml) and washed with dil hydrochloric acid (5%), then the organic layer was separated and the aqueous layer was re-extracted with dichloromethane (2×50 ml). The combined organic layers were washed with satd aq sodium bicarbonate (100 ml) and water (100 ml), dried and evaporated to give a colourless oil. The crude product was columned (5:1 petrol/ethyl acetate) to give 2,2-dimethylpropionic acid 5-hydroxypentyl ester (**12**) as a colourless oil (15.1 g, 84%) [Found $[M+Na]^+$: 211.1302; $C_{10}H_{20}O_3Na$ requires: 211.1305], which showed δ_H (250 MHz, $CDCl_3$): 4.01 (2H, t, *J* 6.4 Hz), 3.58 (2H, t, *J* 6.4 Hz), 2.37 (1H, br s), 1.67–1.49 (4H, m), 1.44–1.32 (2H, m), 1.14 (9H, s); δ_C (62.5 MHz, $CDCl_3$): 178.6, 64.2, 62.3, 38.6, 32.1, 28.3, 27.1, 22.1; ν_{max}: 3379, 2937, 1729 cm^{-1}.

3.1.5. 2,2-Dimethylpropionic acid 5-bromopentyl ester (13). *N*-Bromosuccinimide (15.5 g, 87.2 mmol) was added in portions over 15 min to a stirred solution of ester **12** (13.1 g, 69.6 mmol) and triphenylphosphine (21 g, 80 mmol) in dichloromethane (240 ml) at 0 °C. After stirring at room temperature for 1 h, when TLC showed no starting material, it was quenched with satd aq sodium meta-bisulfate (200 ml). The aqueous layer was re-extracted with dichloromethane (2×50 ml). The combined organic layers were washed with water, dried and evaporated to give a residue. This was treated with 1:1 petrol/ether (100 ml) and refluxed for 30 min, then the triphenylphosphine oxide was filtered off and washed with petrol/ether (50 ml). The filtrate was evaporated and the residue chromatographed (10:2 petrol/ether) to give 2,2-dimethylpropionic acid 5-bromopentyl ester (**13**) (16.04 g, 92%) as a colourless oil [Found $[M+Na]^+$: 273.0449; $C_{10}H_{19}O_2{}^{79}BrNa$ requires: 273.0461], which showed δ_H (500 MHz, $CDCl_3$): 4.07 (2H, t, *J* 6.3 Hz), 3.41 (2H, t, *J* 6.65 Hz), 1.88 (2H, pent, *J* 6.9 Hz), 1.66 (2H, pent, *J* 6.9 Hz), 1.52 (2H, pent, *J* 6.9 Hz), 1.19 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.5, 63.9, 38.7, 33.4, 32.2, 27.7, 27.1, 24.5; ν_{max}: 2959, 2849, 1728, 1480, 1154, 771 cm^{-1}.

3.1.6. 2,2-Dimethylpropionic acid 5-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentyl ester (14). Anhydrous potassium carbonate (18 g, 130 mmol) was added to a stirred solution of ester **13** (15 g, 59.7 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (10.7 g, 60 mmol) in acetone (150 ml) at room temperature. The mixture was stirred vigorously at 40 °C for 3 h, then at room temperature for 16 h, then worked as above to give a pale yellow oil, 2,2-dimethylpropionic acid 5-(1-phenyl-1*H*-tetrazol-5-sulfanyl)pentyl ester (20.2 g, 97%) [Found

[M+H]$^+$: 349.1675; $C_{17}H_{25}N_4O_2S$ requires: 349.1693], which showed δ_H (500 MHz, $CDCl_3$): 7.58–7.51 (5H, m), 4.04 (2H, t, *J* 6.65 Hz), 3.39 (2H, t, *J* 7.6 Hz), 1.86 (2H, pent, *J* 7.55 Hz), 1.67 (2H, pent, *J* 6.6 Hz), 1.51 (2H, pent, *J* 6.97 Hz), 1.17 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.5, 154.3, 133.7, 130.0, 129.8, 123.8, 63.8, 38.7, 33.0, 28.7, 28.0, 27.1, 24.9; ν_{max}: 2971, 1725, 1156, 762, 694 cm^{-1}. This was used for next step without purification. To a vigorously stirred solution of the above ester (32.5 g, 93.27 mmol) in tetrahydrofuran (220 ml) and industrial methylated spirits (270 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (18 g, 14.56 mmol) in ice cold 35% w/w hydrogen peroxide (50 ml). A similar solution was added three times at 0.5 h intervals (total 72 g of heptamolybdate in hydrogen peroxide (200 ml) was added). The mixture was stirred for 16 h at room temperature then worked up as above to give a yellow oil. Chromatography (1:1 petrol/ethyl acetate) gave 2,2-dimethylpropionic acid 5-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentyl ester (**14**) as a thick pale yellow oil (35 g, 99%) [Found [M+H]$^+$: 381.1590; $C_{17}H_{25}N_4O_4S$ requires: 381.1591], which showed δ_H (500 MHz, $CDCl_3$): 7.69–7.67 (2H, m), 7.64–7.57 (3H, m), 4.06 (2H, t, *J* 6.3 Hz), 3.74 (2H, distorted t, *J* 7.9 Hz), 2.03–1.97 (2H, m), 1.7 (2H, pent, *J* 6.3 Hz), 1.58 (2H, pent, *J* 6.95 Hz), 1.18 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.4, 153.4, 132.9, 131.4, 129.7, 125.0, 63.5, 55.8, 38.7, 28.0, 27.1, 24.7, 21.7; ν_{max}: 2968, 1723, 1497, 1343, 1156, 764 cm^{-1}.

3.1.7. 2,2-Dimethylpropionic acid 17-bromoheptadecyl ester (15). Lithium hexamethyldisilazide (38 ml, 40.2 mmol, 1.06 M THF) was added dropwise to a stirred solution of ester **14** (14.1 g, 37 mmol) and 12-bromododecanal (9.58 g, 36.5 mmol) in dry tetrahydrofuran (150 ml) under nitrogen at −10 °C. The reaction was exothermic and the temperature rose to −5 °C. The mixture was allowed to reach room temperature and stirred for 16 h when TLC showed no starting material. Work up as above gave a thick yellow oil; chromatography (10:1 petrol/ether) gave *E*/*Z*-2,2-dimethylpropionic acid 17-bromoheptadec-5-enyl ester in ratio 2.7:1 as a colourless oil (10.9 g, 72%). Palladium on carbon (10%) (0.8 g) was added to a stirred solution of the ester (10.9 g, 26.11 mmol) in ethyl acetate (45 ml) and methanol (110 ml) under hydrogen. When no further hydrogen was absorbed, the reaction mixture was worked up as above. Chromatography (5:2 petrol/ether) gave 2,2-dimethylpropionic acid 17-bromoheptadecyl ester (**15**) as a white solid (9.68 g, 88%), mp 36–38 °C [Found [M+Na]$^+$: 441.2321; $C_{22}H_{43}{}^{79}BrO_2Na$ requires: 441.2339], which showed δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.65 Hz), 3.41 (2H, t, *J* 6.65 Hz), 1.85 (2H, pent, *J* 7.25 Hz), 1.62 (2H, pent, *J* 6.6 Hz), 1.42 (2H, pent, *J* 7.25 Hz), 1.38–1.22 (24H, m), 1.2 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.7, 64.5, 38.7, 34.0, 32.8, 29.64, 29.60, 29.55, 29.53, 29.51, 29.4, 29.2, 28.8, 28.6, 28.2, 27.2, 25.9; ν_{max}: 1719 cm^{-1}.

3.1.8. 2,2-Dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-sulfonyl)heptadecyl ester (16). Anhydrous potassium carbonate (5 g, 36.2 mmol) was added to a stirred solution of ester **15** (9.28 g, 22.12 mmol) and 1-phenyl-1*H*-tetrazol-5-thiol (4 g, 22.4 mmol) in acetone (100 ml) at room temperature. After stirring vigorously for 16 h, work up as above gave a brown oil. Chromatography (5:1 petrol/ether) gave 2,2-dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)heptadecyl ester (10.07 g, 88%) as a colourless oil [Found [M+H]$^+$: 517.3563; $C_{29}H_{49}O_2N_4S$ requires: 517.3571], which showed δ_H (500 MHz, $CDCl_3$): 7.59–7.51 (5H, m), 4.04 (2H, t, *J* 6.65 Hz), 3.39 (2H, t, *J* 7.25 Hz), 1.81 (2H, pent, *J* 7.55 Hz), 1.61 (2H, pent, *J* 6.65 Hz), 1.43 (2H, pent, *J* 6.6 Hz), 1.37–1.23 (24H, m), 1.19 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.6, 154.5, 133.7, 130.0, 129.7, 123.8, 64.4, 38.7, 33.3, 29.61, 29.59, 29.58, 29.7, 29.51, 29.49, 29.46, 29.4, 29.2, 29.04, 28.98, 28.6, 28.6, 27.2, 25.9; ν_{max}: 2920, 2851, 1727, 1500, 1159 cm^{-1}.

To a vigorously stirred solution of the above sulfide (9.7 g, 18.77 mmol) in tetrahydrofuran (110 ml) and industrial methylated spirits (110 ml) was added a solution of ammonium heptamolybdate(VI) tetrahydrate (8.5 g, 6.88 mmol) in ice cold 35% w/w hydrogen peroxide (25 ml) at 15 °C. After 1.5 h, further ice cold heptamolybdate (8.5 g) in hydrogen peroxide (25 ml) was added. The mixture was stirred for 16 h at room temperature, diluted with water (250 ml) and worked up as above to give a white solid. Chromatography (1:1 petrol/ethyl acetate) gave 2,2-dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-sulfonyl)heptadecyl ester (**16**) as a white solid (10.1 g, 98%) [Found [M+Na]$^+$: 571.3271; $C_{29}H_{48}N_4O_4SNa$ requires: 571.32885], mp 51–53 °C, which showed δ_H (500 MHz, $CDCl_3$): 7.71–7.69 (2H, m), 7.65–7.58 (3H, m), 4.04 (2H, t, *J* 6.65 Hz), 3.73 (2H, distorted t, *J* 8.2 Hz), 1.98–1.92 (2H, m), 1.62 (2H, pent, *J* 6.6 Hz), 1.49 (2H, pent, *J* 6.9 Hz), 1.39–1.24 (24H, m), 1.20 (9H, s); δ_C (125 MHz, $CDCl_3$): 178.6, 153.5, 133.1, 131.4, 129.7, 125.1, 64.5, 56.0, 38.7, 29.63, 29.61, 29.53, 29.49, 29.4, 29.20, 29.16, 28.9, 28.6, 28.1, 27.2, 25.9, 21.9; ν_{max}: 2922, 1727, 1497, 1463, 1341, 1284, 1153, 762 cm^{-1}.

3.1.9. (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyraldehyde. (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butanol **17** (1.6 g, 7.47 mmol) in dichloromethane (10 ml) was added to a stirred suspension of pyridinium chlorochromate (4.03 g, 18.7 mmol) in dichloromethane (75 ml) at room temperature and stirred vigorously for 3 h, when TLC showed no starting material, then poured into ether (200 ml), filtered through silica and washed well with ether. The filtrate was evaporated to give an oil; chromatography (5:2 petrol/ether) gave (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]butyraldehyde (1.4 g, 88%), $[\alpha]_D^{22}$ +10.14 (*c* 1.45, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.77 (1H, t, *J* 1.9 Hz), 4.07 (1H, dd, *J* 6, 7.85 Hz), 3.87 (1H, br dt, *J* 6.3, 7.85 Hz), 3.67 (1H, t, *J* 7.55 Hz), 2.41–2.39 (2H, m), 1.74–1.67 (1H, m), 1.44 (3H, s), 1.35 (3H, s), 1.1 (3H, d, *J* 6.6 Hz), 0.97 (1H, br dq, *J* 5.65, 8.2 Hz), 0.88 (1H, br dt, *J* 4.75, 8.8 Hz), 0.82–0.75 (1H, m), 0.36 (1H, br q, *J* 5.35 Hz); δ_C (125 MHz, $CDCl_3$): 201.8 (+), 108.6 (+), 76.7 (+), 70.0 (−), 51.3 (−), 28.6 (+), 26.8 (−), 25.7 (+), 23.2 (+), 20.8 (+), 19.2 (+), 8.8 (−); ν_{max}: 1724 cm^{-1}.

3.1.10. (*S*)-18-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]nonadecanoic acid methyl ester (18). Lithium hexamethyldisilazide (10.12 ml, 10.1 mmol, 1 M THF) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic methyl ester (2.74 g, 6.74 mmol) and (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyraldehyde (1.3 g,

6.13 mmol) in dry tetrahydrofuran (30 ml) under nitrogen at −25 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. The mixture was allowed to reach room temperature and stirred for 1 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with petrol/ether (1:1) (3×40 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick oil; chromatography (10:1 petrol/ether) gave a pale yellow oil, (*S*)-18-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]nonadec-15-enoic acid methyl ester (1.2 g, 48%). Dipotassium azodicarboxylate (2.15 g, 11.1 mmol) was added to a stirred solution of the above ester (1 g, 2.22 mmol) in dry THF (15 ml) and methanol (7 ml) at 10 °C under nitrogen, resulting in a yellow suspension. Glacial acetic acid (3 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C and quenched slowly with satd aq ammonium chloride (5 ml), then extracted with petrol/ether (1:1) (2×50 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; however, the ^{1}H NMR spectra showed that there was still starting material left. The procedure was repeated for another 16 h and the residue was purified by chromatography (10:1 petrol/ethyl acetate) to give (*S*)-18-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]nonadecanoic acid methyl ester (**18**) as a colourless oil, which solidified later (0.62 g, 62%) [Found [M+Na]$^+$: 475.3759; $C_{28}H_{52}O_4Na$ requires: 475.3758], $[\alpha]_D^{22}$ −11.75 (*c* 1.07, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.13–4.09 (1H, m), 3.74–3.71 (2H, m), 3.68 (3H, s), 2.32 (2H, t, *J* 7.55 Hz), 1.63 (2H, br pent, *J* 7.25 Hz), 1.46 (3H, s), 1.37 (3H, s), 1.35–1.2 (28H, m), 1.01 (4H, br s), 0.92 (1H, br dq, *J* 5.3, 8.8 Hz), 0.84 (1H, dt, *J* 4.75, 8.85 Hz), 0.71–0.66 (1H, m), 0.24 (1H, br q, *J* 5.35 Hz); δ_C (125 MHz, $CDCl_3$): 174.4, 108.3, 77.9 (−), 70.0 (+), 51.4 (−), 37.4 (+), 34.1 (+), 33.3 (−), 30 (+), 29.7 (+), 29.6 (+), 29.5 (+), 29.3 (+), 29.2 (+), 27.2 (+), 26.9 (−), 25.8 (−), 25.0 (+), 23.9 (−), 20.0 (−), 19.2 (−), 9.1 (+); ν_{max}: 1730 cm^{-1}.

3.1.11. *cis*-(*S*)-18-((1*R*,2*R*)-2-Formylcyclopropyl)nonadecanoic acid methyl ester (19). Periodic acid (0.9 g, 3.98 mmol) was added to a stirred solution of ester **18** (0.6 g, 1.33 mmol) in dry ether (40 ml) under nitrogen at room temperature. After 16 h, TLC showed no starting material. The precipitate was filtered, washed with ether and the solvent was evaporated. Chromatography (10:1 petrol/ethyl acetate) gave *cis*-(*S*)-18-((1*R*,2*R*)-2-formylcyclopropyl)-nonadecanoic acid methyl ester (**19**) (0.4 g, 80%) [Found [M+Na]$^+$: 403.3202; $C_{24}H_{44}O_3Na$ requires: 403.3183], $[\alpha]_D^{22}$ +1.98 (*c* 1.19, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.33 (1H, d, *J* 5.65 Hz), 3.67 (3H, s), 2.3 (2H, t, *J* 7.85 Hz), 1.93–1.87 (1H, m), 1.61 (2H, br pent, *J* 7.2 Hz), 1.44–1.15 (32H, m), 1.05 (3H, d, *J* 6.6 Hz); δ_C (125 MHz, $CDCl_3$): 201.8 (−), 174.3, 51.4 (−), 37.4 (+), 34.1 (+), 32.3 (−), 32.0 (−), 29.9 (+), 29.7 (+), 29.64 (+), 29.60 (+), 29.5 (+), 29.3 (+), 29.2 (+), 28.7 (−), 26.8 (+), 24.9 (+), 20.1 (−), 13.6 (+); ν_{max}: 1740, 1706 cm^{-1}.

3.1.12. Attempted epimerization[43] of aldehyde (19). Sodium methoxide (0.13 g, 2.43 mmol) was added to a stirred solution of *cis*-aldehyde **18** (0.37 g, 0.97 mmol) in methanol (30 ml) and tetrahydrofuran (10 ml). This was refluxed for 56 h, cooled to room temperature and quenched with satd aq ammonium chloride (20 ml), and extracted with ether (3×50 ml). The combined organic layers were dried, evaporated and no product was obtained (gave a white gel, which was not soluble in $CDCl_3$).

3.1.13. *tert*-Butyl-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane. Triethylamine (5.66 g, 56.1 mmol) was added to a stirred solution of alcohol **17** (6 g, 28.03 mmol) in dry dichloromethane (150 ml). After 10 min, *tert*-butyldiphenylsilyl chloride (10 g, 36.4 mmol) in dichloromethane (20 ml) was added, followed by dimethylaminopyridine (0.5 g) in dry dichloromethane (5 ml). The mixture was stirred for 4 h, when TLC showed no starting material, quenched with water (50 ml) and extracted with dichloromethane (3×100 ml). The combined organic layers were washed with brine and water, and dried to give a residue. This was purified by chromatography (5:1 petrol/ether) to give a colourless oil *tert*-butyl-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (11.02 g, 87%) [Found M$^+$: 452.2747; $C_{28}H_{40}O_3Si$ requires: 452.2747], $[\alpha]_D^{22}$ −7.8 (*c* 1.54, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 7.69–7.67 (4H, m), 7.47–7.39 (6H, m), 4.19 (1H, dd, *J* 6, 8 Hz), 3.79–3.63 (4H, m), 1.76–1.7 (1H, m), 1.48 (3H, s), 1.41–1.35 (1H, m), 1.35 (3H, s), 1.07 (9H, s), 0.97 (3H, d, *J* 6.3 Hz), 0.96–0.915 (1H, m), 0.91–0.85 (2H, m), 0.74–0.68 (1H, m), 0.29 (1H, br q, *J* 5.1 Hz); δ_C (125 MHz, $CDCl_3$): 135.6, 135.5, 133.80, 133.78, 129.64, 129.62, 127.68, 127.66, 108.3, 77.8, 70.1, 61.5, 40, 29.7, 26.8, 25.7, 23.9, 19.6, 19.3, 19.2, 9.3; ν_{max}: 2930, 2858, 1111, 1062 cm^{-1}.

3.1.14. *cis*-(1*R*,2*R*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (21). Periodic acid (12.6 g, 55.3 mmol) was added to a stirred solution of *tert*-butyl-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (10 g, 22.12 mmol) in dry ether (150 ml) under nitrogen at room temperature. The mixture was stirred for 16 h when TLC showed no starting material. The precipitate was filtered then washed with ether and the solvent was evaporated to give a residue; chromatography (10:2 petrol/ether) gave *cis*-(1*R*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (**21**) (8 g, 96%) [Found: C 75.5, H 8.6; $C_{24}H_{32}O_2Si$ requires: C 75.74, H 8.47], $[\alpha]_D^{22}$ +3.66 (*c* 1.64, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.32 (1H, d, *J* 6 Hz), 7.69–7.66 (4H, m), 7.47–7.40 (6H, m), 3.73–3.64 (2H, m), 1.91–1.86 (1H, m), 1.72–1.63 (2H, m), 1.5–1.45 (1H, m), 1.33–1.17 (3H, m), 1.07 (9H, s), 1.06 (3H, d, *J* 6.3 Hz); δ_C (125 MHz, $CDCl_3$): 201.5, 135.6, 133.9, 133.8, 129.6, 127.6, 61.4, 39.8, 31.7, 29.3, 28.6, 26.9, 19.9, 19.1, 13.8; ν_{max}: 1703 cm^{-1}.

3.1.15. *trans*-(1*S*,2*R*)-2-[(*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (22). Sodium methoxide (0.937 g, 17.36 mmol) was added to a stirred solution of *cis*-aldehyde **21** (6 g, 15.78 mmol) in methanol (250 ml) and refluxed for 56 h.[43] The mixture was cooled to room temperature and quenched with satd aq ammonium chloride (100 ml), and the product was extracted with ether (3×150 ml). The combined organic layers were

dried and evaporated to give a thick oil, which solidified later. Chromatography (5:2 petrol/ether) gave *trans*-(1*S*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (**22**) (1.16 g, 19%) [Found $[M+Na]^+$: 403.2075; $C_{24}H_{32}O_2NaSi$ requires: 403.2064], $[\alpha]_D^{22}$ +22.9 (*c* 1.28, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.00 (1H, d, *J* 5.35 Hz), 7.71–7.67 (4H, m), 7.47–7.39 (6H, m), 3.77 (1H, br dt, *J* 6.3, 10.4 Hz), 3.71 (1H, dt, *J* 6.65, 10.4 Hz), 1.76–1.71 (1H, m), 1.7–1.67 (1H, m), 1.56–1.5 (1H, m), 1.32–1.24 (3H, m), 1.07 (9H, s), 0.99 (3H, d, *J* 6.3 Hz), 0.96–0.93 (1H, m); δ_C (125 MHz, $CDCl_3$): 200.9, 135.6, 135.5, 135.2, 134.8, 133.9, 133.8, 129.6, 127.73, 127.69, 127.66, 61.4, 39.3, 33.3, 30.1, 29.2, 26.9, 26.6, 19.3, 19.2, 19.0, 13.6; ν_{max}: 1707 cm^{-1}. The second fraction (1:1 petrol/ethyl acetate) was (1*S*,2*R*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropanecarbaldehyde (1.16 g, 52%), which showed δ_H (500 MHz, $CDCl_3$): 8.97 (1H, d, *J* 5.65 Hz), 3.73–3.63 (2H, m), 2.15 (1H, br s), 1.76–1.73 (1H, m), 1.71–1.65 (1H, m), 1.59–1.53 (1H, m), 1.35–1.30 (1H, m), 1.29–1.25 (1H, m), 1.21–1.13 (1H, m), 1.03 (3H, d, *J* 7 Hz), 0.95 (1H, m); δ_C (125 MHz, $CDCl_3$): 201.1 (−), 60.2 (+), 39.4 (+), 33.5 (−), 30.3 (−), 28.9 (−), 19.6 (−), 13.3 (+); ν_{max}: 3414 cm^{-1}. The alcohol was protected as before to give the title compound in 81% yield. There was less than 5% of the cis-isomer.

3.1.16. 2,2-Dimethylpropionic acid 18-{(1*S*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (23). Lithium hexamethyldisilazide (14.1 ml, 14.1 mmol, 1 M THF) was added dropwise to a stirred solution of sulfone (**16**) (5.15 g, 9.4 mmol) and aldehyde **22** (3.25 g, 8.55 mmol) in dry tetrahydrofuran (50 ml) under nitrogen at −20 °C. The reaction was exothermic and the temperature rose to −10 °C, resulting in a yellow solution. The mixture was allowed to reach room temperature, stirred for 2 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with 1:1 petrol/ether (3×50 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick oil. Chromatography (10:1 petrol/ether) gave a pale yellow oil, 2,2-dimethylpropionic acid 18-{(1*R*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester (4.5 g, 78%), as a 2.7:1 mixture of two isomers [Found $[M+Na]^+$: 725.5303; $C_{46}H_{74}O_3NaSi$ requires: 725.5299]; δ_H (500 MHz, $CDCl_3$) (major isomer): 7.70–7.68 (4H, m), 7.46–7.37 (6H, m), 5.38 (1H, br dt, *J* 6.6, 15 Hz), 4.94 (1H, br dd, *J* 8.5, 15 Hz), 4.1 (2H, t, *J* 6.6 Hz), 3.85–3.74 (2H, m), 1.94 (2H, br q, *J* 6.3 Hz), 1.67–1.58 (4H, m), 1.4–1.26 (25H, br s), 1.23 (9H, s), 1.17–1.12 (1H, m), 1.07 (9H, s), 1.04–0.97 (1H, m), 0.93 (3H, d, *J* 6.6 Hz), 0.89–0.87 (1H, m), 0.47–0.41 (3H, m); δ_H (500 MHz, $CDCl_3$) (minor isomer): 5.26 (1H, br dt, *J* 7.25, 10.8 Hz), 4.73 (1H, br t, *J* 10.8 Hz), 2.13 (1H, m). The remaining signals were obscured by the major isomer.

Method A: dipotassium azodicarboxylate (3.3 g, 17.1 mmol) was added to a stirred solution of 2,2-dimethylpropionic acid 18-{(1*R*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester (4.5 g, 6.4 mmol) in dry THF (30 ml) and methanol (15 ml) at 10 °C under nitrogen, giving a yellow suspension. Glacial acetic acid (4 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C, quenched slowly with satd aq ammonium chloride (5 ml) and extracted with 1:1 petrol/ether (2×100 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; ^1H NMR showed that there was still starting material left. The procedure was repeated twice for 16 h and the residue was chromatographed (10:1 petrol/ether) to give 2,2-dimethylpropionic acid 18-{(1*S*,2*R*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (**23**) as a white solid (4.5 g, 99.5%) [Found $[M+Na]^+$: 727.5477; $C_{46}H_{76}O_3NaSi$ requires: 727.5456], $[\alpha]_D^{22}$ +5.7 (*c* 1.93, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 7.69–7.66 (4H, m), 7.43–7.36 (6H, m), 4.07 (2H, t, *J* 6.6 Hz), 3.80–3.72 (2H, m), 1.74–1.68 (1H, m), 1.65–1.59 (2H, br pent, *J* 6.5 Hz), 1.56–1.49 (1H, m), 1.36–1.23 (31H, br s), 1.20 (9H, s), 1.17–1.12 (1H, m), 1.05 (9H, s), 0.94–0.84 (4H, including br s, *δ* 0.88), 0.46–0.40 (1H, m), 0.18–0.137 (2H, m), 0.12–0.09 (1H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 135.6 (+), 134.2, 129.5 (+), 127.5 (+), 64.46 (−), 62.35 (−), 40.21 (−), 38.72, 34.77 (+), 34.34 (−), 29.7 (−), 29.63 (−), 29.58 (−), 29.56 (−), 29.5 (−), 29.2 (−), 28.6 (−), 27.2 (+), 26.9 (+), 25.9 (−), 19.8 (+), 19.2, 18.6 (+), 10 (−); ν_{max}: 2920, 2850, 1730 cm^{-1}.

Method B: triisopropylbenzenesulfonyl hydrazide (0.63 g, 2.13 mmol) was added to the above ester (0.5 g, 0.712 mmol) in tetrahydrofuran (20 ml) at room temperature and stirred for 24 h at 45–50 °C, followed by the addition of another mol. equivalent of triisopropylbenzenesulfonyl hydrazide then stirring for 24 h. After diluting with petrol/ether (1:1) (100 ml) and quenching with aq sodium hydroxide (2%, 20 ml), the organic layer was separated and the aqueous layer was re-extracted with petrol/ether (2×25 ml). The combined organic layers were washed with brine, dried and evaporated. Chromatography on silica eluting with 10:1 petrol/ether gave **23** (0.42 g, 85%), which showed identical spectra to those above.

3.1.17. 2,2-Dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-hydroxypropyl)cyclopropyl]octadecyl ester. Tetra-*n*-butylammonium fluoride (9.6 ml, 9.6 mmol, 1 M solution) was added with stirring to ester **23** (4.5 g, 6.4 mmol) in dry tetrahydrofuran (50 ml) at 5 °C. The mixture was stirred for 16 h at room temperature, when TLC showed no starting material, then evaporated, quenched with water (30 ml) and extracted with dichloromethane (3×50 ml). The combined organic layers were dried and evaporated to give a thick oil. Chromatography (5:0.5 petrol/ethyl acetate) gave 2,2-dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-hydroxypropyl)cyclopropyl]octadecyl ester (2.63 g, 89%) [Found $[M+Na]^+$: 489.4300; $C_{30}H_{58}O_3Na$ requires: 489.4278], $[\alpha]_D^{22}$ +11.02 (*c* 1.27, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.6 Hz), 3.77–3.68 (2H, br m), 1.75–1.68 (1H, sext, *J* 6.65 Hz), 1.65–1.60 (2H, m), 1.58–1.51 (1H, m), 1.35–1.24 (32H, br m), 1.19 (9H, s), 1.17–1.11 (1H, m), 0.95 (3H, d, *J* 6.65 Hz), 0.90–0.81 (1H, m), 0.51–0.45 (1H, m), 0.25–0.13 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 64.5 (+), 61.4 (+), 40.4 (+), 38.7, 35.0 (−), 34.3 (+), 29.7 (+), 29.62 (+), 29.58 (+), 29.54 (+), 29.51 (+), 29.2 (+), 28.6 (+), 27.2 (−), 25.9 (+), 19.8 (−), 18.7 (−), 10.6 (+); ν_{max}: 3397, 1731 cm^{-1}.

3.1.18. 2,2-Dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (24). 2,2-Dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-hydroxypropyl)cyclopropyl]octadecyl ester (2.5 g, 5.5 mmol) in dichloromethane (20 ml) was added to a suspension of pyridinium chlorochromate (2.96 g, 13.7 mmol) in dichloromethane (100 ml). The mixture was stirred vigorously at room temperature for 3 h, when TLC showed no starting material, then diluted with ether (250 ml) and filtered through a pad of Celite and then a pad of silica. The silica was washed with ether. The combined filtrate was evaporated to give a residue, which was purified by chromatography (5:0.5 petrol/ethyl acetate) to give a colourless oil, 2,2-dimethylpropionic acid 18-[(1*S*,2*R*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (**24**) (2.07 g, 83%) [Found [M+Na]$^+$: 487.4100; $C_{30}H_{56}O_3Na$ requires: 487.4122], $[\alpha]_D^{22}$ +17.1 (*c* 1.82, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 9.8 (1H, t, *J* 2.5 Hz), 4.06 (2H, t, *J* 6.6 Hz), 2.52 (1H, ddd, *J* 2.5, 6.0, 15.75 Hz), 2.39 (1H, ddd, *J* 2.5, 7.55, 15.75 Hz), 1.63 (2H, pent, 6.6 Hz), 1.4–1.24 (32H, m), 1.2 (9H, s), 1.20–1.14 (1H, m), 1.03 (3H, d, *J* 6.6 Hz), 0.54–0.47 (1H, m), 0.36–0.23 (3H, m); δ_C (125 MHz, $CDCl_3$): 202.8, 178.6, 64.4 (−), 51.4 (−), 38.7, 34.1 (−), 33.9 (+), 29.7 (−), 29.64 (−), 29.62 (−), 29.58 (−), 29.55 (−), 29.5 (−), 29.2 (−), 28.6 (−), 27.2 (+), 25.9 (−), 25.6 (+), 19.9 (+), 18.8 (+), 11.4 (−); ν_{max}: 2922, 2853, 1729 cm^{-1}.

3.1.19. (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-Dimethylpropionyloxy)-octadecyl]cyclopropyl}nonadecanoic acid methyl ester (25). Lithium hexamethyldisilazide (6.4 ml, 6.4 mmol, 1 M THF) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)-pentadecanoic methyl ester **11** (1.73 g, 4.26 mmol) and ester **24** (1.8 g, 3.87 mmol) in dry tetrahydrofuran (30 ml) under nitrogen at −30 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. The mixture was allowed to reach room temperature and stirred for 1 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with petrol/ether (1:1) (3×30 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil. Chromatography (10:1 petrol/ether) gave a pale yellow oil, (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadec-15-enoic acid methyl ester (1.5 g, 55%) as a mixture of two isomers in ratio 2.2:1 [Found [M+Na]$^+$: 725.6446; $C_{46}H_{86}O_4Na$ requires: 725.6418]; δ_H (500 MHz, $CDCl_3$) (major isomer): 5.47–5.37 (2H, m), 4.06 (2H, t, *J* 6.65 Hz), 3.68 (3H, s), 2.3 (2H, t, *J* 7.5 Hz), 2.17–2.12 (1H, m), 2.06–1.92 (3H, m), 1.67–1.61 (5H, m), 1.38–1.25 (51H, m), 1.27 (9H, s), 0.91 (3H, d, *J* 6.6 Hz), 0.78–0.73 (1H, m), 0.50–0.45 (1H, m), 0.30–0.12 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 174.3, 131.4, 128.8, 64.5, 51.4, 34.4, 34.1, 32.7, 29.72, 29.70, 29.68, 29.65, 29.63, 29.60, 29.57, 29.55, 29.53, 29.47, 29.27, 29.24, 29.22, 29.17, 28.6, 27.2, 25.9, 25.7, 25.0, 19.2, 18.6, 10.8; ν_{max}: 2921, 1731, 1479 cm^{-1}; δ_H (500 MHz, $CDCl_3$) (minor isomer): 1.12–1.18 (1H, m), 0.88–0.85 (3H, d, *J* 6.6 Hz), 0.86 (1H, m); δ_C (125 MHz, $CDCl_3$): 130.4, 128.4, 34.7, 34.4, 29.4, 29.1, 27.3, 25.8, 22.65, 22.62, 22.3, 19.4, 15.3, 14.3, 14.1, 14.0, 11.4, 10.7. The remaining signals were obscured by the major isomer. Dipotassium azodicarboxylate (3.3 g, 17.1 mmol) was added to a stirred solution of the above ester (1.2 g, 1.71 mmol) in dry THF (15 ml) and methanol (7 ml) at 10 °C under nitrogen, giving a yellow suspension. Glacial acetic acid (2 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C, quenched slowly with satd aq ammonium chloride (5 ml) and extracted with 1:1 petrol/ether (2×50 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; the ^{1}H NMR spectrum showed that there was still starting material left. The procedure was repeated for another 16 h and the residue was purified by chromatography (10:1 petrol/ether) to give a white solid, (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]-cyclopropyl}nonadecanoic acid methyl ester (**25**) (0.78 g, 65%) [Found [M+Na]$^+$: 727.6560; $C_{46}H_{88}O_4Na$ requires: 727.6575], $[\alpha]_D^{22}$ +3.7 (*c* 1.03, $CHCl_3$), mp 47–49 °C; δ_H (500 MHz, $CDCl_3$): 4.06 (2H, t, *J* 6.6 Hz), 3.68 (3H, s), 2.32 (2H, t, *J* 7.6 Hz), 1.64 (4H, m), 1.4–1.24 (60H, br m), 1.2 (9H, s), 0.91 (3H, d, *J* 6.6 Hz), 0.69–0.63 (1H, m), 0.48–0.41 (1H, m), 0.21–0.08 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.62, 174.31, 64.45 (+), 51.39 (−), 38.71, 38.11 (−), 37.41 (+), 34.47 (+), 34.11 (+), 30.06 (+), 29.70 (+), 29.64 (+), 29.56 (+), 29.51 (+), 29.45 (+), 29.25 (+), 29.22 (+), 29.15 (+), 28.61 (+), 27.25 (+), 27.19 (−), 26.13 (−), 25.90 (+), 24.95 (+), 19.67 (−), 18.61 (−), 10.48 (+); ν_{max}: 2918, 1733 cm^{-1}.

3.1.20. (*S*)-18-[(1*R*,2*S*)-2-(18-Hydroxyoctadecyl)cyclopropyl]-nonadecanoic acid methyl ester. (*S*)-18-{(1*R*,2*S*)-2-[18-(2,2-Dimethylpropionyloxy)octadecyl]cyclopropyl}-nonadecanoic acid methyl ester (0.27 g, 0.383 mmol) in tetrahydrofuran (5 ml) was added to a stirred solution of potassium hydroxide (0.31 g, 5.59 mmol) in methanol (10 ml), tetrahydrofuran (10 ml) and water (1.5 ml) at room temperature. The mixture was stirred and refluxed at 70 °C for 4 h, when TLC showed no starting material, then cooled to 5 °C, when a white precipitate formed, filtered on a sinter, then washed with ether (2×20 ml). The precipitate was dissolved in hot water and acidified with H_2SO_4 (10%) and the product was extracted with hot petrol/ether (1:1). The organic layer was dried and evaporated to give a white solid, (*S*)-18-[(1*R*,2*S*)-2-(18-hydroxyoctadecyl)-cyclopropyl]nonadecanoic acid (0.22 g, 95%). This was treated with excess diazomethane solution in ether and left to stand for 24 h at room temperature, then the solvent was evaporated to give a solid, which was recrystallized from petrol/ether to give a white solid, (*S*)-18-[(1*R*,2*S*)-2-(18-hydroxyoctadecyl)cyclopropyl]nonadecanoic acid methyl ester (0.19 g, 84%) [Found [M+Na]$^+$: 643.35991; $C_{41}H_{80}O_3Na$ requires: 643.6000], $[\alpha]_D^{22}$ +5.12 (*c* 1.21, $CHCl_3$), mp 65–67 °C; δ_H (500 MHz, $CDCl_3$): 3.67 (3H, s, OCH_3), 3.64 (2H, t, *J* 6.65 Hz, CH_2OH), 2.3 (2H, t, *J* 7.55 Hz, CH_2CO), 1.63–1.54 (6H, m, satd alkane), 1.45–1.21 (57H, m, satd alkane), 1.2–1.15 (2H, br dq, *J* 3.15, 7.2 Hz, satd alkane), 0.9 (3H, d, *J* 6.6 Hz, α-Me), 0.71–0.63 (1H, m, $CHCH_3$), 0.48–0.42 (1H, m, CH-*trans*-cyclopropane), 0.21–0.09 (3H, m, CH and CH_2-*trans*-cyclopropane); δ_C (125 MHz, $CDCl_3$): 174.36, 63.1 (+), 51.42 (−), 38.12 (−), 37.42 (+), 34.47 (+), 34.12 (+), 32.81 (+), 30.06 (+), 29.71 (+), 29.66 (+), 29.60 (+), 29.46 (+), 29.43 (+), 29.26 (+), 29.15 (+), 27.25 (+), 26.14 (−), 25.73 (+), 24.96 (+), 19.69 (−), 18.62 (−), 10.49 (+); ν_{max}: 3340, 1733 cm^{-1}.

3.1.21. [(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]methanol. Tetra-*n*-butylammonium fluoride (79.2 ml, 79.2 mmol) was added to a stirred solution of *tert*-butyl-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropylmethyl]diphenylsilane (25 g, 60.9 mmol) in dry tetrahydrofuran (150 ml), at 0 °C under nitrogen. The mixture was allowed to reach room temperature, stirred for 16 h when TLC showed no starting material, cooled to 5 °C and quenched with satd aq ammonium chloride (50 ml) and extracted with ethyl acetate (3×200 ml). The combined organic layers were washed with brine (100 ml) and water (100 ml), dried and evaporated to give an oil. Chromatography (1:1 petrol/ethyl acetate) gave [(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]methanol (9.54 g, 91%) [Found $[M+NH_4]^+$: 190.1442; $C_9H_{20}O_3N$ requires: 190.1443], $[\alpha]_D^{22}$ −16.2 (*c* 0.995, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.99 (1H, dd, *J* 2.12, 7.6 Hz), 3.6 (1H, br t, *J* 7.3 Hz), 3.52 (1H, dt, *J* 5.5, 7.3 Hz), 3.4 (1H, dd, *J* 6.7, 11.3 Hz), 3.32 (1H, dd, *J* 7, 11.3 Hz), 2.8 (1H, br s), 1.34 (3H, s), 1.25 (3H, s), 1.00–0.86 (1H, m), 0.84–0.74 (1H, m), 0.57 (1H, dt, *J* 4.9, 8.55 Hz), 0.46 (1H, dt, *J* 5.17, 8.55 Hz); δ_C (125 MHz, $CDCl_3$): 108.7, 78.9, 68.9, 65.4, 26.6, 25.4, 18.8, 17.5, 7.8; ν_{max}: 3436, 2984, 2934 cm^{-1}.

3.1.22. (1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)-cyclopropanecarbaldehyde. [(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]methanol (9 g, 52.32 mmol) in dichloromethane (50 ml) was added to a suspension of pyridinium chlorochromate (23.7 g, 109.8 mmol) in dichloromethane (400 ml) and stirred vigorously. After 2 h, when TLC showed no starting material, it was cooled to room temperature, poured into ether (500 ml), then the precipitate was filtered through silica and washed with ether. The filtrate was evaporated to give a yellow oil; chromatography (1:1 petrol/ethyl acetate) gave (1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropanecarbaldehyde (8.1 g, 91%) [Found $[M+H]^+$: 171.1023; $C_9H_{15}O_3$ requires: 171.1021], $[\alpha]_D^{22}$ −66 (*c* 1.33, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.08 (1H, d, *J* 4.9 Hz), 4.1 (1H, dd, *J* 5.9, 7.7 Hz), 3.78 (1H, br q, *J* 6.7 Hz), 3.65 (1H, br t, *J* 6.9 Hz), 1.89–1.81 (1H, m), 1.73–1.63 (1H, m), 1.45 (3H, s), 1.37–1.29 (1H, m), 1.33 (3H, s), 1.26–1.16 (1H, m); δ_C (125 MHz, $CDCl_3$): 199.9, 109.4, 76.4, 69.0, 26.52, 26.49, 25.5, 23.7, 11.7; ν_{max}: 1709 cm^{-1}.

3.1.23. (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid methyl ester (27). Methyl-(triphenylphosphoranylidene)acetate (19.1 g, 47 mmol) was added in portions to a stirred solution of (1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropanecarbaldehyde (8 g, 47 mmol) in toluene (100 ml) at 10 °C. The mixture was allowed to reach room temperature and stirred for 24 h when GLC showed no starting material. The solvent was evaporated and the residue was treated with petrol/ether (1:1) (200 ml) and refluxed for 10 min. The precipitate was filtered off and washed with petrol/ether (100 ml). The solvent was evaporated and the residue was purified by chromatography eluting with petrol/ethyl acetate (5:2) to give (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]acrylic acid methyl ester (**27**) (8.4 g, 79%) [Found $[M+Na]^+$: 249.1095; $C_{12}H_{18}O_4Na$ requires: 249.1097], $[\alpha]_D^{22}$ −75 (*c* 1.16, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 6.43 (1H, dd, *J* 10.1, 15.5 Hz), 5.85 (1H, d, *J* 15.5 Hz), 4.05 (1H, dd, *J* 5.2, 7.3 Hz), 3.76–3.62 (5H, m, including s at δ 3.68), 1.58–1.47 (1H, m), 1.4 (3H, s), 1.32 (3H, s), 1.22–1.15 (1H, m), 1.07 (1H, dt, *J* 5.2, 8.55 Hz), 0.89 (1H, dt, *J* 5, 8.55 Hz); δ_C (125 MHz, $CDCl_3$): 166.8, 151.7, 118.5, 109.1, 77.5, 69.0, 51.3, 26.6, 25.5, 24.4, 18.4, 12.8; ν_{max}: 1720, 1647 cm^{-1}. There was less than 5% of the cis-isomer.

3.1.24. Addition of methyl magnesium bromide to (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid methyl ester (27). Methyl magnesium bromide (35.4 ml, 106.2 mmol) was added dropwise to a stirred suspension of copper bromide (7.6 g, 53.1 mmol) in dry tetrahydrofuran (250 ml) at −40 °C under nitrogen. The mixture was stirred for 30 min then (*E*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]acrylic acid methyl ester (8 g, 35.4 mmol) in dry tetrahydrofuran (50 ml) was added dropwise at −30 °C. The mixture was allowed to reach −5 °C over 2 h, when GLC showed no starting material, then quenched slowly with satd aq ammonium chloride (50 ml) at −30 °C. The product was extracted with ethyl acetate (3×250 ml). The combined organic layers were washed with brine (100 ml), dried and evaporated to give a brown oil. Chromatography (5:2 petrol/ethyl acetate) gave a mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]butyric acid methyl ester and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyric acid methyl ester in ratio 1:1 (**28**) (6 g, 70%) [Found $[M+Na]^+$: 265.1414; $C_{13}H_{22}O_4Na$ requires: 265.1410], $[\alpha]_D^{22}$ −12.3 (*c* 1.14, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 4.05 (1H, dd, *J* 6.3, 7.6 Hz), 4.02 (1H, dd, *J* 6, 12 Hz), 3.67 (3H, s), 3.667 (1H, t, *J* 7.9 Hz), 3.66 (3H, s), 3.62 (1H, t, *J* 7.9 Hz), 3.94 (1H, br dd, *J* 3.45, 7.9 Hz), 3.45 (1H, br dd, *J* 3.15, 7.9 Hz), 2.4 (1H, br dd, *J* 6.3, 15 Hz), 2.35 (1H, br dd, *J* 6.3, 15 Hz), 2.26 (2H, br dd, *J* 7.85, 14.8 Hz), 1.43 (3H, s), 1.42 (3H, s), 1.36–1.30 (2H, m), 1.33 (3H, s), 1.32 (3H, s), 1.03 (3H, d, *J* 6 Hz), 1.02 (3H, d, *J* 6.5 Hz), 0.82–0.77 (1H, m), 0.76–0.71 (1H, m), 0.61–0.55 (2H, m), 0.54–0.50 (3H, m), 0.49–0.44 (1H, m); δ_H (500 MHz, C_6D_6): 3.87 (1H, dd, *J* 6, 7.9 Hz), 3.81 (1H, dd, *J* 6, 7.9 Hz), 3.54 (1H, t, *J* 7.6 Hz), 3.5 (1H, t, *J* 7.6 Hz), 3.36 (1H, dt, *J* 6.3, 7.6 Hz), 3.35 (6H, s), 3.33 (1H, dt, *J* 6, 7.3 Hz), 2.21 (1H, dd, *J* 6.3, 14.8 Hz), 2.15 (1H, dd, *J* 6.3, 14.8 Hz), 2.06 (1H, dd, *J* 7.85, 14.8 Hz), 2.02 (1H, dd, *J* 7.55, 14.8 Hz), 1.54 (6H, s), 1.44 (3H, s), 1.43 (3H, s), 1.32–1.24 (2H, m), 1.00 (3H, d, *J* 6.6 Hz), 0.93 (3H, d, *J* 6.9 Hz), 0.77–0.72 (1H, m), 0.64–0.58 (1H, m), 0.57–0.52 (2H, m), 0.42–0.34 (3H, m), 0.28 (1H, dt, *J* 4.7, 8.2 Hz); δ_C (125 MHz, $CDCl_3$): 173.2, 173.1, 108.9, 108.8, 79.9, 79.8, 69.3, 69.2, 51.43, 51.41, 41.5, 41.4, 34.9, 34.8, 26.8, 25.75, 25.71, 25.69, 22.2, 22.1, 20.3, 20.00, 19.8, 19.7, 9.7, 9.2; ν_{max}: 1738 cm^{-1}.

3.1.25. Reduction of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butyric acid methyl ester and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)-cyclopropyl]butyric acid methyl ester. The mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butyric acid methyl ester and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)-cyclopropyl]butyric acid methyl ester (5.5 g, 22.7 mmol) in dry tetrahydrofuran (30 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.73 g, 45.4 mmol) in tetrahydrofuran (150 ml) at room temperature under

nitrogen. The mixture was refluxed for 1 h when TLC showed no starting material, then cooled to 0 °C and quenched with satd aq sodium sulfate (40 ml) until a white solid was formed. The precipitate was filtered off and washed with tetrahydrofuran (2×50 ml). The filtrate was evaporated to give a crude product which was purified by chromatography (1:1 petrol/ethyl acetate) to give a mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol (4.47 g, 92%) [Found $[M+Na]^+$: 237.1454; $C_{12}H_{22}O_3Na$ requires: 237.1461], $[\alpha]_D^{22}$ −13.9 (*c* 1.69, $CHCl_3$), which showed δ_H (mixture, C_6D_6, 500 MHz): 3.84 (1H, dd, *J* 5.35, 6 Hz), 3.85 (1H, dd, *J* 5.1, 6 Hz), 3.55 (1H, t, *J* 7.85 Hz), 3.54 (1H, t, *J* 7.6 Hz), 3.48–3.32 (6H, m), 1.49–1.40 (8H, including two s at δ 1.44 and 1.42 (each 3H)), 1.35–1.23 (8H, including two s at δ 1.33 and 1.32 (each 3H)), 0.97 (2H, br s), 0.84 (3H, d, *J* 6.95 Hz), 0.77 (3H, d, *J* 6.3 Hz), 0.74–0.67 (2H, m), 0.66–0.61 (1H, m), 0.53–0.43 (3H, m), 0.33–0.24 (2H, m), 0.21–0.13 (2H, m); δ_C (mixture, C_6D_6, 125 MHz): 109.5, 109.4, 80.5, 79.9, 70.1, 69.9, 61.3, 61.2, 40.9, 40.8, 35.2, 35.0, 27.8, 27.7, 26.7, 26.6, 23.3, 23.2, 21.3, 20.7, 20.4, 10.8, 9.3; ν_{max}: 3410 cm^{-1}.

3.1.26. *tert*-Butyl-{(*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane and *tert*-butyl-{(*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (29). The mixture of (*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butan-1-ol and (*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol (3 g, 14 mmol) in dry DMF (15 ml) was added to a stirred solution of imidazole (1.43 g, 21 mmol) in dry DMF (40 ml) at 5 °C under nitrogen. The mixture was stirred for 20 min then *tert*-butyldiphenylsilylchloride (4.62 g, 16.8 mmol) was added, then allowed to reach room temperature and stirred for 4 h when TLC showed no starting material. The solvent was evaporated under high vacuum and the residue was diluted with dichloromethane (100 ml) and water (50 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 water and brine, dried and evaporated to give a residue, which was purified by chromatography on silica eluting with 5:1 petrol and ethyl acetate to give a mixture of *tert*-butyl-{(*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane and *tert*-butyl-{(*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}diphenylsilane (**29**) (5.5 g, 87%) [Found $[M+Na]^+$: 475.2628; $C_{28}H_{40}O_3SiNa$ requires: 475.2639], $[\alpha]_D^{22}$ −6.8 (*c* 137, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (8H, m), 7.45–7.38 (12H, m), 4.05 (1H, dd, *J* 6, 8.2 Hz), 3.96 (1H, dd, *J* 6, 8 Hz), 3.79–3.64 (5H, m), 3.57 (1H, t, *J* 8 Hz), 3.46–3.40 (2H, m), 1.70–1.63 (2H, sext, *J* 6.5 Hz), 1.56–1.48 (2H, m), 1.45 (3H, s), 1.43 (3H, s), 1.35 (3H, s), 1.34 (3H, s), 1.30–1.25 (2H, m), 1.06 (9H, s), 1.05 (9H, s), 0.91 (3H, d, *J* 6.3 Hz), 0.907 (3H, d, *J* 6.6 Hz), 0.72–0.63 (2H, m), 0.56–0.47 (3H, m), 0.46–0.34 (3H, m); δ_H (500 MHz, C_6D_6): 7.79–7.76 (8H, m), 7.25–7.22 (12H, m), 3.83 (1H, dd, *J* 6, 7.85 Hz), 3.78 (1H, dd, *J* 6, 7.6 Hz), 3.76–3.67 (4H, m), 3.54 (1H, t, *J* 7.85 Hz), 3.5 (1H, t, *J* 7.6 Hz), 3.42–3.38 (1H, br q, *J* 7.25 Hz), 3.37–3.33 (1H, br dt, *J* 6.3, 7.55 Hz), 1.67–1.60 (2H, m), 1.50–1.44 (2H, m), 1.44 (3H, s), 1.42 (3H, s), 1.33 (3H, s), 1.32 (3H, s), 1.17 (18H, s), 0.86–0.82 (5H, br m), 0.76 (3H, d, *J* 6.6 Hz), 0.63–0.58 (1H, m), 0.54–0.5 (1H, m), 0.49–0.44 (2H, m), 0.36–0.33 (1H, dt, *J* 5.05, 8.2 Hz), 0.35–0.25 (1H, m), 0.21–0.14 (2H, m); δ_C (125 MHz, $CDCl_3$): 135.5, 134.1, 133.9, 129.6, 129.5, 127.60, 127.58, 127.56, 108.8, 108.6, 80.5, 80.0, 69.3, 69.2, 62.0, 61.8, 39.8, 39.7, 34.1, 34.0, 30.9, 26.9, 26.8, 26.5, 25.8, 25.7, 23.5, 22.8, 22.5, 20.2, 19.8, 19.5, 19.4, 19.2, 10.2, 8.8; δ_C (125 MHz, C_6D_6): 136.6, 135.10, 135.05, 130.60, 130.55, 80.5, 79.8, 70.2, 70.1, 63.1, 62.9, 40.9, 40.8, 35.2, 34.9, 27.8, 27.7, 26.74, 26.72, 23.4, 23.22, 21.4, 20.6, 20.5, 20.4, 20.1, 20.0, 10.7, 9.2; ν_{max}: 2932, 2858, 1111, 1062 cm^{-1}.

3.1.27. (1*R*,2*S*)-2-[(*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde and (1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl] cyclopropanecarbaldehyde. Periodic acid (6.3 g, 27.6 mmol) was added to a stirred mixture of *tert*-butyl-{(*R*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butoxy}-diphenylsilane and *tert*-butyl-{(*S*)-3-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxo-lan-4-yl)cyclopropyl]butoxy}diphenylsilane (5 g, 11.1 mmol) in dry ether (100 ml) under nitrogen at room temperature. After stirring for 16 h, TLC showed no starting material. The precipitate was filtered, washed with ether and the solvent was evaporated to give a residue. Chromatography (10:2 petrol/ethyl acetate) gave a mixture of (1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde and (1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (3.86 g, 92%) [Found $[M+Na]^+$: 403.2048; $C_{24}H_{32}O_2SiNa$ requires: 403.2064], $[\alpha]_D^{22}$ −17.85 (*c* 1.26, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 8.98 (2H, d, *J* 5.65 Hz), 7.68–7.65 (8H, m), 7.45–7.37 (12H, m), 3.82–3.66 (4H, m), 1.74–1.47 (7H, m), 1.35–1.18 (7H, m), 1.06 (18H, s), 0.97 (3H, d, *J* 6.6 Hz), 0.95 (3H, d, *J* 6.65 Hz); δ_H (500 MHz, C_6D_6): 8.74 (1H, d, *J* 3.15 Hz), 8.73 (1H, d, *J* 2.85 Hz), 7.78–7.73 (8H, m), 7.28–7.19 (12H, m), 3.67–3.57 (4H, m), 1.5–1.39 (3H, m), 1.38–1.29 (2H, m), 1.28–1.22 (1H, m), 1.15 (9H, s), 1.14 (9H, s), 0.87–0.76 (6H, m), 0.71 (3H, d, *J* 6.3 Hz), 0.67 (3H, d, *J* 6.3 Hz), 0.49–0.45 (1H, m), 0.35–0.31 (1H, br ddd, *J* 4.4, 6.0, 10.1 Hz); δ_C (125 MHz, $CDCl_3$): 200.9, 200.8, 135.5, 134.8, 133.9, 133.8, 129.6, 127.64, 127.61, 61.5, 61.4, 39.4, 39.3, 33.5, 33.3, 30.1, 29.3, 29.25, 29.19, 26.8, 26.5, 19.5, 19.3, 19.2, 14.6, 13.5; δ_C (125 MHz, C_6D_6): 199.6, 199.5, 136.6, 136.5, 135.8, 134.91, 134.90, 134.8, 130.64, 130.63, 62.6, 62.5, 40.3, 40.26, 34.2, 34.1, 30.6, 29.6, 29.3, 29.0, 27.7, 27.4, 20.1, 20.0, 14.7, 13.3; ν_{max}: 1703 cm^{-1}.

3.1.28. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (30). Lithium hexamethyldisilazide (16.6 ml, 16.6 mmol, 1 M THF) was added dropwise to a stirred solution of 2,2-dimethylpropionic acid 17-(1-phenyl-1*H*-tetrazol-5-sulfonyl)heptadecyl ester **16** (6.06 g, 11.1 mmol) and a mixture of (1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde and (1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropanecarbaldehyde (3.5 g, 9.21 mmol) in dry tetrahydrofuran (50 ml) under nitrogen at −15 °C. The reaction was exothermic and the

temperature rose to −5 °C giving in a yellow solution. The mixture was allowed to reach room temperature and stirred for 2 h when TLC showed no starting material, cooled to 0 °C and quenched with satd aq ammonium chloride (10 ml). The product was extracted with 1:1 petrol/ether (3×50 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil. Chromatography (10:1 petrol/ether) gave a pale yellow oil, (*E*/*Z*)-2,2-dimethylpropionic acid 18-{(1*S*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester and 2,2-dimethylpropionic acid 18-{(1*S*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylpropylsilanyloxy)-1-methylpropyl]cyclopropyl}octadec-17-enyl ester (5.17 g, 80%). Dipotassium azodicarboxylate (3.9 g, 20.1 mmol) was added to a stirred solution of the above mixture (4.7 g, 6.69 mmol) in dry THF (30 ml) and methanol (15 ml) at 10 °C under nitrogen, resulting in a yellow suspension. Freshly distilled glacial acetic acid (4 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C and quenched slowly with satd aq ammonium chloride (5 ml). The product was extracted with petrol/ether (1:1) (2×100 ml). The combined organic layers were washed with water (20 ml), dried and evaporated to give a thick oil, which solidified slowly; however, the ^{1}H NMR spectrum showed that there was still starting material left. The procedure was repeated twice for 16 h and the residue was purified by chromatography (10:1 petrol/ether) to give 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylpropylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (**30**) as a white solid (3.77 g, 80%) [Found [M+Na]$^+$: 727.5470; $C_{46}H_{76}O_3SiNa$ requires: 727.5456], $[\alpha]_D^{22}$ −6.1 (*c* 1.23, $CHCl_3$). The mixture showed δ_H (500 MHz, $CDCl_3$): 7.68–7.67 (8H, m), 7.43–7.37 (12H, m), 4.06 (4H, t, *J* 6.65 Hz), 3.79–3.7 (4H, m), 1.74–1.68 (2H, m), 1.65–1.6 (4H, m), 1.57–1.47 (2H, m), 1.38–1.24 (64H, m), 1.21 (18H, s), 1.18–1.13 (2H, m), 1.06 (9H, s), 1.05 (9H, s), 0.86 (3H, br s), 0.84 (3H, br s), 0.42–0.31 (2H, m), 0.19–0.04 (6H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 135.6, 134.2, 129.4, 127.5, 67.9, 64.5, 62.3, 62.2, 40.2, 40.0, 38.7, 34.8, 34.7, 34.4, 34.35, 29.7, 29.63, 29.56, 29.5, 29.4, 29.2, 28.6, 27.2, 26.9, 25.9, 25.88, 25.6, 20.0, 19.8, 19.2, 18.6, 17.5, 11.8, 10.6; ν_{max}: 2920, 2850, 1732 cm^{-1}.

3.1.29. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*R*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (31) and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (32). Tetra-*n*-butylammonium fluoride (7.45 ml, 7.45 mmol) was added to a stirred solution of 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*R*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester and 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-[(*S*)-3-(*tert*-butyldiphenylsilanyloxy)-1-methylpropyl]cyclopropyl}octadecyl ester (3.5 g, 4.97 mmol) in dry tetrahydrofuran (50 ml) at 0 °C under nitrogen. The mixture was stirred at room temperature for 16 h when TLC showed no starting material, cooled to 5 °C and quenched with satd aq ammonium chloride (50 ml) and the product extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with brine (50 ml) and water (50 ml), dried and evaporated to give an oil. Chromatography (5:1 petrol/ethyl acetate) gave as the first fraction 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*R*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (**31**) as a white solid (1.1 g, 48%) [Found [M+Na]$^+$: 489.4290; $C_{30}H_{58}O_3Na$ requires: 489.4278], $[\alpha]_D^{22}$ −11.29 (*c* 1.08, $CHCl_3$), mp 34–36 °C, which showed δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.6 Hz), 3.76–3.67 (2H, m), 1.74–1.68 (1H, br sext., *J* 6.65 Hz), 1.64–1.58 (2H, pent, *J* 6.65 Hz), 1.57–1.51 (1H, m), 1.49 (1H, br s), 1.35–1.23 (31H, br m), 1.19 (9H, s), 1.13 (1H, m), 0.95 (3H, d, *J* 6.65 Hz), 0.88–0.82 (1H, m), 0.51–0.44 (1H, m), 0.25–0.13 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 64.4 (+), 61.3 (+), 40.4 (+), 38.7, 34.9 (−), 34.3 (+), 29.7 (+), 29.6 (+), 29.57 (+), 29.5 (+), 29.48 (+), 29.2 (+), 28.6 (+), 27.2 (−), 25.9 (+), 19.8 (−), 18.7 (−), 10.6 (+); ν_{max}: 3396, 1730 cm^{-1}. The second fraction was 2,2-dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropyl]-octadecyl ester (**32**), a white solid (0.92 g, 40%) [Found [M+Na]$^+$: 489.4288; $C_{30}H_{58}O_3Na$ requires: 489.4278], $[\alpha]_D^{22}$ −4.03 (*c* 1.29, $CHCl_3$), mp 44–46 °C, which showed δ_H (500 MHz, $CDCl_3$): 4.04 (2H, t, *J* 6.65 Hz), 3.76 (1H, br dd, *J* 6.3, 10.5 Hz), 3.71 (1H, br dd, *J* 6.9, 10.5 Hz), 1.72–1.65 (1H, br sext., *J* 6.95 Hz), 1.64–1.59 (2H, br pent, *J* 6.6 Hz), 1.56–1.51 (1H, m), 1.46 (1H, br s), 1.36–1.26 (31H, br m), 1.29 (9H, s), 1.09–1.02 (1H, m), 0.99 (3H, d, *J* 6.6 Hz), 0.90–0.82 (1H, m), 0.46–0.39 (1H, m), 0.29–2.00 (3H, m); δ_C (125 MHz, $CDCl_3$): 178.6, 64.5 (+), 61.4 (+), 40.3 (+), 38.7, 35.2 (−), 34.3 (+), 29.7 (+), 29.6 (+), 29.54 (+), 29.50 (+), 29.2 (+), 28.6 (+), 27.2 (−), 25.9 (+), 25.8 (−), 20.3 (−), 17.6 (−), 11.9 (+); ν_{max}: 3396, 1730 cm^{-1}.

3.1.30. 2,2-Dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*R*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*R*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (0.7 g, 1.5 mmol) was dissolved in dichloromethane (10 ml) and added to a suspension of pyridinium chlorochromate (0.8 g, 3.75 mmol) in dichloromethane (50 ml). The mixture was stirred vigorously at room temperature for 3 h when TLC showed no starting material was left, diluted with diethyl ether (150 ml) and filtered through a pad of Celite and then through a pad of silica. The silica was washed with ether. The combined filtrate was evaporated to give a residue, which was purified by chromatography (5:0.5 petrol/ethyl acetate) to give a colourless oil, 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*R*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester, which solidified later (0.62 g, 89%) [Found [M+Na]$^+$: 487.4122; $C_{30}H_{56}O_3Na$ requires: 487.4122], $[\alpha]_D^{22}$ −16.4 (*c* 1.82, $CHCl_3$), mp 28–30 °C; δ_H (500 MHz, $CDCl_3$): 9.78 (1H, t, *J* 2.5 Hz), 4.05 (2H, t, *J* 6.6 Hz), 2.50 (1H, ddd, *J* 2.5, 6.0, 15.75 Hz), 2.38 (1H, ddd, *J* 2.5, 7.6, 15.75 Hz), 1.62 (2H, br pent, *J* 6.6 Hz), 1.36–1.25 (32H, m), 1.2 (9H, s), 1.16–1.02 (4H, including d, *J* 6.6 Hz, δ 1.03), 0.53–0.46 (1H, m), 0.35–0.22 (3H, m); δ_C (125 MHz, $CDCl_3$): 202.8 (+), 178.6, 64.4 (−), 51.4 (−), 38.7, 34.1 (−), 33.9 (+), 29.7 (−), 29.63 (−), 29.61 (−), 29.58 (−), 29.5 (−), 29.49 (−), 29.2 (−), 28.6 (−), 27.2 (+), 25.9 (−), 25.6 (+), 19.9 (+), 18.8 (+), 11.4 (−); ν_{max}: 2920, 2850, 1728 cm^{-1}.

3.1.31. 2,2-Dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester. 2,2-Dimethylpropionic acid 18-{(1*R*,2*S*)-2-((*S*)-3-hydroxy-1-methylpropyl)cyclopropyl]octadecyl ester (0.7 g, 1.5 mmol)

was dissolved in dichloromethane (10 ml) and added to a suspension of pyridinium chlorochromate (0.8 g, 3.75 mmol) in dichloromethane (50 ml). The mixture was stirred vigorously at room temperature for 3 h when TLC showed no starting material, diluted with diethyl ether (150 ml) and worked up as above to give 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (0.63 g, 90%), [Found $[M+Na]^+$: 487.4106; $C_{30}H_{56}O_3Na$ requires: 487.4122], $[\alpha]_D^{22}$ −0.011 (*c* 1.23, $CHCl_3$), mp 31–32 °C; δ_H (500 MHz, $CDCl_3$): 9.78 (1H, t, *J* 2.5 Hz), 4.05 (2H, t, *J* 6.6 Hz), 2.49 (1H, ddd, *J* 2.2, 6.0, 15.45 Hz), 2.35 (1H, ddd, *J* 2.5, 7.6, 15.45 Hz), 1.61 (2H, br pent, *J* 6.6 Hz), 1.38–1.24 (32H, m), 1.19 (9H, s), 1.09–1.02 (4H, including d, *J* 6.65 Hz, *δ* 1.05), 0.54–0.48 (1H, m), 0.34–0.29 (1H, m), 0.27–0.21 (2H, m); δ_C (125 MHz, $CDCl_3$): 202.9 (+), 178.6, 64.4 (−), 51.3 (−), 38.7, 34.2 (−), 34.0 (+), 29.7 (−), 29.6 (−), 29.54 (−), 29.51 (−), 29.2 (−), 28.6 (−), 27.2 (+), 25.9 (−), 25.6 (+), 20.3 (+), 18.5 (+), 11.9 (−); ν_{max}: 2920, 2850, 1728 cm^{-1}.

3.1.32. Methyl (*R*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadecanoate (33). Lithium hexamethyldisilazide (1.87 ml, 1.87 mmol, 1 M THF) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic methyl ester (0.558 g, 1.375 mmol) and 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*R*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester **11** (0.58 g, 1.25 mmol) in dry tetrahydrofuran (20 ml) under nitrogen at −15 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. This was stirred at room temperature for 1 h when TLC showed no starting material, then cooled to 0 °C, quenched with satd aq ammonium chloride (10 ml) and extracted with 1:1 petrol/ether (3×30 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil; chromatography (10:1 petrol/ether) gave a pale yellow oil, (*E*/*Z*)-(*R*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadec-15-enoic acid methyl ester (0.57 g, 65%) as a 2.2:1 mixture of isomers. Dipotassium azodicarboxylate (1.38 g, 7.12 mmol) was added to a stirred solution of the ester (0.5 g, 0.712 mmol) in dry THF (15 ml) and methanol (7 ml) at 10 °C under nitrogen, resulting in a yellow suspension. Glacial acetic acid (2 ml) in dry THF (4 ml) was added dropwise over 48 h, after which a white precipitate had formed. The mixture was cooled to 0 °C, quenched slowly with satd aq ammonium chloride (5 ml), then extracted with petrol/ether (1:1) (2×50 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 spectrum showed that there was still starting material left. The procedure was repeated twice for 24 h and the residue was purified by chromatography (10:1 petrol/ether) to give (*R*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)-octadecyl]cyclopropyl}nonadecanoic acid methyl ester (**33**) as a white solid (0.4 g, 80%), mp 47–49 °C, [Found $[M+Na]^+$: 727.6579; $C_{46}H_{88}O_4Na$ requires: 727.6575], $[\alpha]_D^{22}$ −5.08 (*c* 1.16, $CHCl_3$); δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.65 Hz, CH_2OCO), 3.67 (3H, s, OCH_3), 2.30 (2H, t, *J* 7.27 Hz, CH_2CO), 1.62 (4H, br pent, *J* 7 Hz, $CH_2CH_2CH_2CO$), 1.4–1.22 (59H, br m, satd alkane), 1.2 (9H, s, $COC(CH_3)_3$), 1.18–1.15 (1H, m, satd alkane), 0.90 (3H, d, *J* 6.9 Hz, α-CH_3), 0.693–0.637 (1H, m, $CHCH_3$), 0.48–0.43 (1H, m, CH-*trans*-cyclopropane), 0.216–0.087 (3H, m, CH and CH_2-*trans*-cyclopropane); δ_C (125 MHz, $CDCl_3$): 178.56, 174.25, 64.42 (+), 51.35 (−), 38.68, 38.11 (−), 37.41 (+), 34.46 (+), 34.07 (+), 30.05 (+), 29.69 (+), 29.63 (+), 29.588 (+), 29.55 (+), 29.51 (+), 29.44 (+), 29.24 (+), 29.21 (+), 29.13 (+), 28.59 (+), 27.24 (+), 27.17 (−), 26.11 (−), 25.88 (+), 24.93 (+), 19.677 (−), 18.60 (−), 10.47 (+); ν_{max}: 2918, 1733 cm^{-1}.

3.1.33. Methyl (*S*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadecanoate (34). Lithium hexamethyldisilazide (1.6 ml, 1.6 mmol, 1 M) was added dropwise to a stirred solution of 15-(1-phenyl-1*H*-tetrazol-5-sulfonyl)pentadecanoic methyl ester **11** (0.48 g, 1.375 mmol) and 2,2-dimethylpropionic acid 18-[(1*R*,2*S*)-2-((*S*)-1-methyl-3-oxopropyl)cyclopropyl]octadecyl ester (0.50 g, 1.07 mmol) in dry tetrahydrofuran (20 ml) under nitrogen at −15 °C. The reaction was exothermic and the temperature rose to 0 °C resulting in a yellow solution. This was allowed to reach room temperature and stirred for 1 h when TLC showed no starting material, then worked up as above. Chromatography gave (*E*/*Z*)-(*S*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl}nonadec-15-enoic acid methyl ester (0.52 g, 70%). Hydrogenation and purification as above gave methyl (*S*)-18-{(1*S*,2*R*)-2-[18-(2,2-dimethylpropionyloxy)octadecyl]cyclopropyl]-nonadecanoate (**34**) as a white solid (0.4 g, 80%) [Found $[M+Na]^+$: 727.6552; $C_{46}H_{88}O_4Na$ requires: 727.6575], $[\alpha]_D^{22}$ −3.87 (*c* 1.16, $CHCl_3$), mp 60–62 °C; δ_H (500 MHz, $CDCl_3$): 4.05 (2H, t, *J* 6.65 Hz, CH_2OCO), 3.67 (3H, s, OCH_3), 2.30 (2H, t, *J* 7.25 Hz, CH_2CO), 1.62 (4H, br pent, *J* 6.3 Hz, $CH_2CH_2CH_2CO$), 1.43–1.23 (59H, br m, satd alkane), 1.2 (9H, s, $COC(CH_3)_3$), 1.07–1.01 (1H, m, satd alkane), 0.93 (3H, d, *J* 6.65 Hz, α-Me), 0.69–0.64 (1H, m, $CHCH_3$), 0.41–0.35 (1H, m, CH-*trans*-cyclopropane), 0.23–0.21 (1H, m, CH-*trans*-cyclopropane), 0.197–0.14 (2H, m, CH_2-*trans*-cyclopropane); δ_C (125 MHz, $CDCl_3$): 178.61, 174.30, 64.45 (+), 51.38 (−), 38.71, 38.05 (−), 37.34 (+), 34.48 (+), 34.1 (+), 30.08 (+), 29.69 (+), 29.63 (+), 29.588 (+), 29.55 (+), 29.51 (+), 29.44 (+), 29.24 (+), 29.21 (+), 29.13 (+), 28.59 (+), 27.24 (+), 27.17 (−), 26.11 (−), 25.90 (+), 24.95 (+), 19.90 (−), 17.34 (−), 11.81 (+); ν_{max}: 2918, 1733 cm^{-1}.

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