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The synthesis of one enantiomer of the α-methyl-*trans*-cyclopropane unit of mycolic acids

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Abstract—We report the synthesis of a single enantiomer of an α-methyl-*trans*-cyclopropane unit present in a number of mycolic acids and its incorporation into a reported 1,2-dialkylcyclopropane meromycolate that contains one *cis*-1,2-dialkylcyclopropane and one α-methyl-*trans*-1,2-dialkylcyclopropane.
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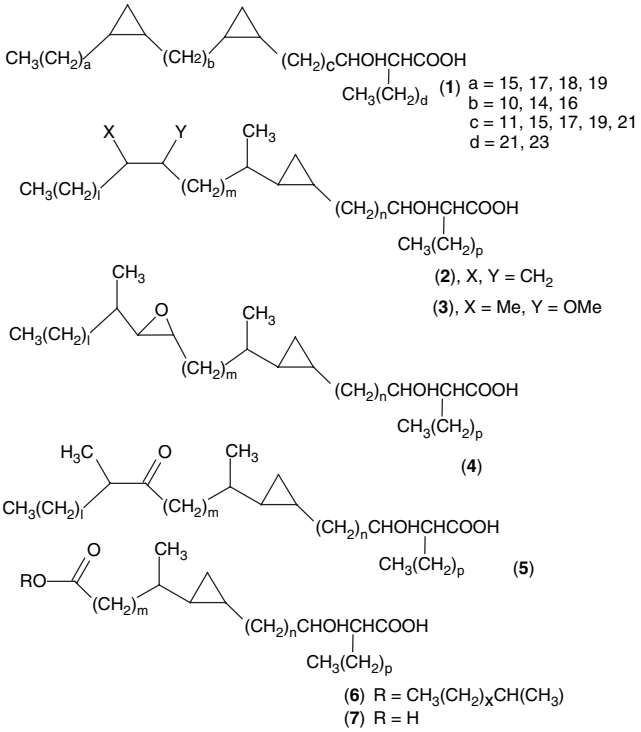
1. Introduction

Mycobacterial cell walls show unusually low permeability, a factor, which contributes to their resistance to therapeutic agents. This is believed to be due to an exceptionally thick mono-layer formed by the packing of C_{60}–C_{90} fatty acids (esters).[1] These 'mycolic acids', exemplified by structures such as **1**–**5**, show a variety of structural features including just *cis*-cyclopropanes **1** and α-methyl-*trans*-cyclopropanes **2** (α-mycolic acids),[2] various combinations of either above type of cyclopropane with α-methyl-β-methoxy groups (methoxymycolates), e.g., (**3**) and α-methyl-β-keto-groups (ketomycolates), e.g., (**5**), as well as molecules containing *cis*-alkene, α-methyl-*trans*-alkene[3–10] and α-methyl-*trans*-epoxy groups, e.g., **4** (l, m, n, p are all long alkyl chains).[7,11a–c] In each case there is a common β-hydroxyacid functionality, while the acids are generally present as mixtures of various chain lengths.[8,9] The balance of these structures, which is dependant on the mycobacterial species, changes membrane permeability and fluidity and hence resistance to a therapeutic agent.[11d] Although the hydroxyacid grouping is known to be of *R*,*R*-configuration for a number of bacteria,[12] 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 hydroxyacid in mycolic acids **3** is *S*,*S* based on the additivity of optical rotations,[12c,7b] while other reports identify an *R*-stereochemistry for the three stereo-centres of the α-methyl-*trans*-epoxy unit in **4**.[13,7]

Mycolic acids containing *trans*-cyclopropanes at the position in the chain closest to the hydroxyacid have a particular effect on the cell wall and therefore on the sensitivity of mycobacterial species to hydrophobic antibiotics.[5] Although the ratio of *trans*- to *cis*-cyclopropanes in ketomycolic acids can in some cases exceed 6, and ratios of 0.2–0.6 are common in methoxymycolic acids, the proportion of *trans*-mycolates **2** to cis-isomers **1** in α-mycolic acids is generally either zero or below 10%.[9] In addition to those structures



Scheme 1.

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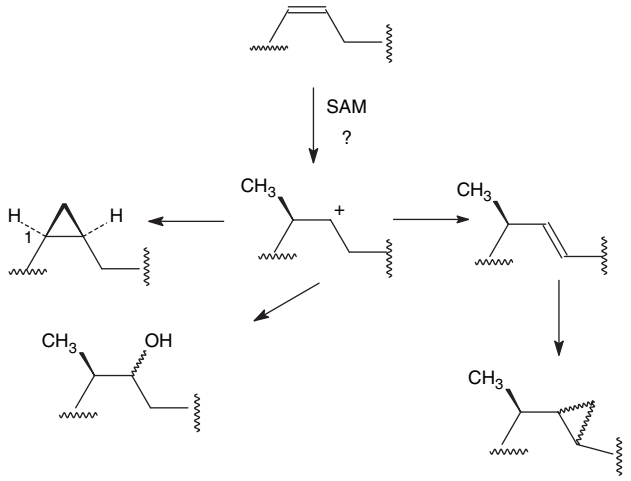
described above, two other types of α-methyl-*trans*-cyclopropane containing mycolic acid derivative, the wax esters **6**[10] and diacids **7** have been reported, while *Mycobacterium gordonae* contains derivatives of the dicarboxylate **7** (Scheme 1).[15]

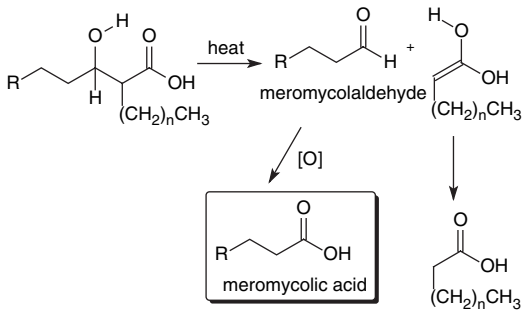
Much is now known about the enzymes that control the biosynthesis of mycolic acids,[16] and a number of proposals have been made to the relationship between routes to the different types, e.g., that the *cis*-cyclopropane unit, the α-methyl-*trans*-cyclopropane and the α-methyl-β-alkoxy unit are formed from a *Z*-alkene through a common cation (Scheme 2).[17] A consequence of this would be that the three sub-units should have a common absolute stereochemistry at the carbon bearing the methyl-group and C-1 of the *cis*-cyclopropane, e.g., Scheme 2.



Scheme 2.

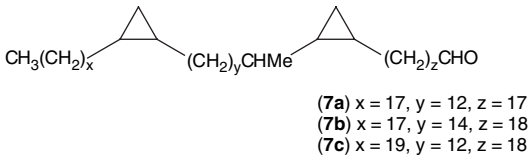
However, labelling studies show that the methyl branches in the α-methyl-*trans*-cyclopropane of mycolic acids from *Mycobacterium tuberculosis* are derived from the 2-position of acetate units, whereas those from *Mycobacterium smegmatis* are derived from C-1.[18] The *cma*A2 gene in virulent *M. tuberculosis* has been shown to be required for the synthesis of *trans*-cyclopropanes in both keto- and methoxymycolates.[19]

One of the standard methods for the characterisation of mycolic acids is thermolysis to fragment the hydroxyacid functionality and to give an aldehyde, or 'meromycolaldehyde' (Scheme 3).[1,2] This can be oxidised to the corresponding 'meromycolic acid'.



Scheme 3.

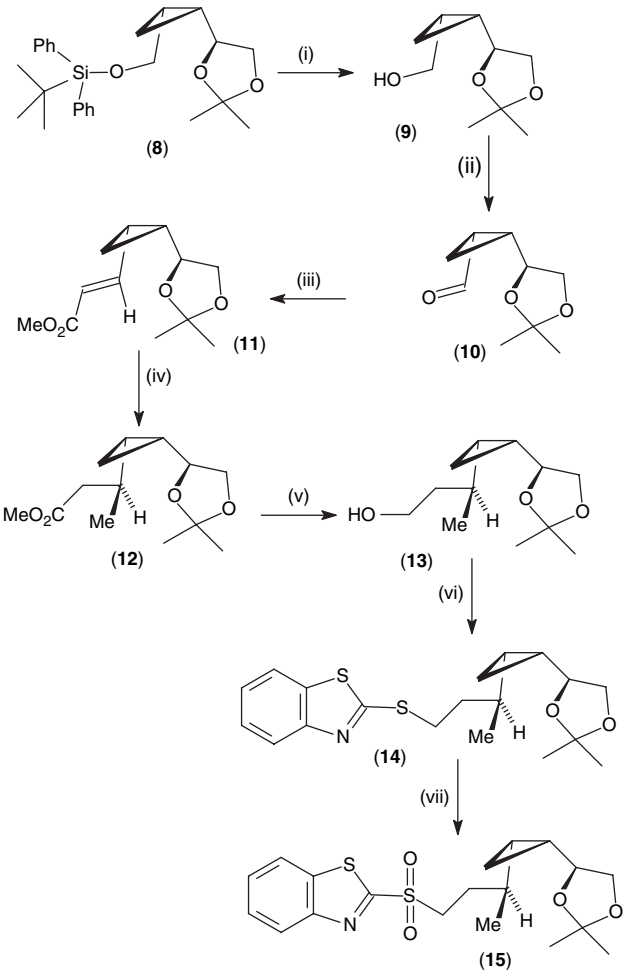
A pioneering paper reported the isolation of a meromycolaldehyde for which structure **7a** (Scheme 4) was proposed as the main component from the thermolysis of the mycolic acids from *Mycobacterium avium*, and proposed that the parent mycolic acid is (**2**, *a*=*c*=17, *b*=12, *d*=21), although it was noted that such a structure would have an odd number of carbons in the main chain.[2a] The assignment was based on MS data and on the presence of a methyl doublet in the NMR spectrum at δ 0.99. Both cyclopropanes were assigned cis-configurations in this paper. In all later examples, the cyclopropane α to the methyl-group is trans, in accord with the postulated biosynthetic pathways (Scheme 2).[1,17] For example, a similar assignment of a doublet at δ 0.99 to a methyl adjacent to a cyclopropane was made in ketomycolates, but now the cyclopropane was assigned as trans.[2b,9] The *M. avium* meromycolyl alcohol had a significantly larger $[\alpha]_D$ than that from *M. tuberculosis* (−1.33 compared to −0.13). Recent detailed studies,[8,9] have shown that the α-mycolic acids from *M. avium* have a principal di-*cis*-cyclopropane component (**1**, *a*=*c*=17, *b*=14, *d*=21) (together with two minor homologues), accompanied by a minor acid with an α-methyl-*trans*-cyclopropane **7b** and a related α-methyl-*trans*-alkene component. These findings may explain the original observation of a methyl branch signal in the low resolution NMR spectrum recorded in the earlier study.[2] These unusual α-mycolic acids have only been identified in members of the *M. avium* complex (**7b**) and *Mycobacterium kansasii* (**7b**,**c**).[8,9]



Scheme 4.

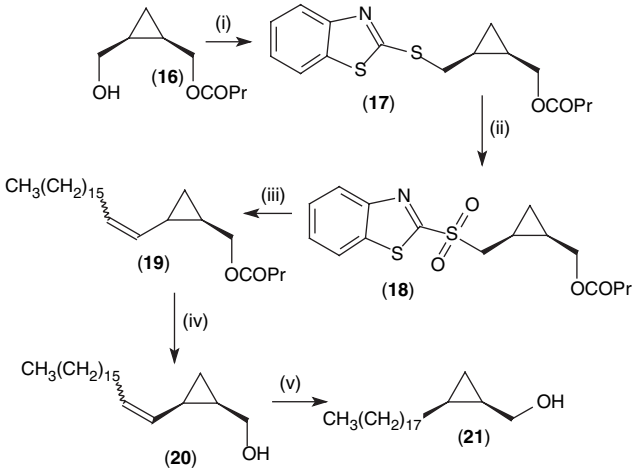
In no case has the absolute stereochemistry of the *trans*-cyclopropane or the relative stereochemistry of this and the adjacent methyl branch been determined. In recent studies, we have reported syntheses of single enantiomers of α-mycolates containing two *cis*-cyclopropanes,[14a,b] and of the corresponding meromycolates.[14c] We now report the preparation of a single α-methyl-*trans*-cyclopropane-containing building block that can be used in the synthesis of a range of mycolic acids and meromycolates containing this subunit; the method can be readily adapted to produce a number of absolute stereochemistries and any appropriate chain length. We also report its application in the preparation of a single enantiomer of **7a**. In separate papers we will report the synthesis of single enantiomers of compounds of type **2**, **3**, **5**, **6** and **7**.

Key to the route presented is the introduction of the α-methyl-cyclopropane fragment. This was achieved (Scheme 5) using the known acetal **8**[20] which was desilylated, oxidised to the corresponding aldehyde **10** and treated with methoxycarbonylmethylene tri-phenylphosphorane in toluene to give mainly **11** (Scheme 6). When toluene was replaced by methanol, a 2:1 mixture of *E*- and *Z*-isomers was obtained. Reaction of the *E*-isomer **11** with methyl magnesium bromide and copper bromide led to a single alkylated product **12**. A trace of a minor compound, probably the isomer with the opposite methyl-group stereochemistry, was also observed (1:15). Moreover, when the mixture of the *E*-alkene **11** with the *Z*-isomer was used, the same product was obtained.



(i) Bu_4NF, THF (85 %); (ii) PCC, CH_2Cl_2 (85 %); (iii) $Ph_3PCH{=}CHCO_2Me$, toluene, (81 %); (iv) MeMgBr, THF (72 %); (v) $LiAlH_4$, THF (88 %); (vi) 2-mercaptobenzthiazole, PPh_3, DEAD, thf (87 %); (vii) ammonium molybdate(VI) tetrahydrate, H_2O_2, methylated spirits (67%)

Scheme 5.



(i) Ph_3P, DEAD, THF, 2-mercaptobenzthiazole (73 %); (ii) $Mo_7O_{24}(NH_4)_6.4H_2O$, H_2O_2, IMS (92 %); (iii) heptadecanal, NaBSA, THF, -20 °C (68 %); (iv) $LiAlH_4$, THF (84 %); (v) H_2NNH_2, $CuSO_4$, $NaIO_4$, CH_3COOH, iPrOH (81 %)

Scheme 6.

Reduction of **12** with lithium aluminium hydride led the corresponding alcohol **13**; the absolute configuration of this was confirmed by X-ray crystallography of the corresponding 3,5-dinitrobenzoate, based on the known configuration of **8** (Fig. 1). The alcohol was converted into sulfide **14** which was oxidised to sulfone **15**; some deprotection of the acetal group occurred during this process, but the diol formed (20%) could be reprotected to give **15** in 95% yield.

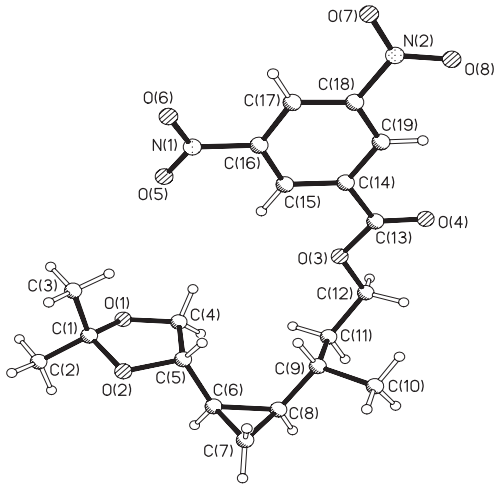


Figure 1. Molecular structure of the 3,5-dinitrobenzoate of **13**.

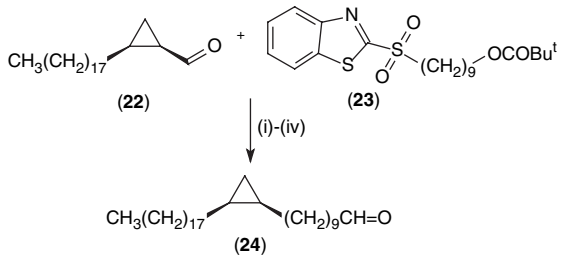
The next stage in the route to **7a** required the alcohol **21**. This was prepared from alcohol **16** (ee>95%, obtained by a modification of a route used by Grandjean),[21,22] which was converted into the sulfone **18**† and then coupled with heptadecanal (prepared by coupling heptylmagnesium bromide with 10-bromo-decanol in the presence of $LiCuCl_4$ to give heptadecanol, followed by PCC oxidation), in a Julia type reaction.[23a] Hydrolysis of the ester **19**, and saturation of the alkene using diimide gave alcohol **21**.[24]

Oxidation of **21** with PCC led to the aldehyde **22** in 85% yield. The sulfone **23** was prepared from nonan-1,9-diol. The diol was monoprotected with 2,2-dimethylpropanoyl (pivalyl) chloride, pyridine and DMAP (50%). The monopivalyl ester was converted into the sulfone by reaction with triphenylphosphine, DEAD and 2-mercaptobenz-thiazole, then oxidation with H_2O_2 and ammonium molybdate(VI) tetra-hydrate (72% overall). Homologation of the aldehyde **22** by reaction with sulfone **23** and sodium hexamethyldisilazide was followed by removal of the ester, saturation of the alkene and oxidation of the alcohol to give the aldehyde **24** (Scheme 7).

The sulfone **15** was condensed with **24** again in a modified Julia reaction,[23a] to form the dicyclopropane **25**. Saturation of the alkene and oxidative cleavage of the acetal group gave the aldehyde **26** which was epimerised using sodium methoxide in methanol to a 22:1 mixture of aldehydes **27** and **26** (Scheme 8).[22,25]

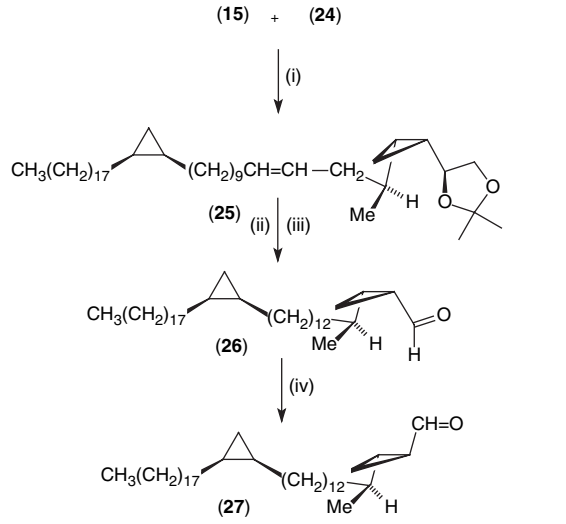
α-Methyl-*trans*-cyclopropanes have previously been obtained by cyclopropanation of 4-methylalk-3-en-1-ols,[26] by 1,3-elimination,[27] and by rearrangement of propargyl ethers.[28]

† The enantiomers of **17** and **18** have already been reported.[14]



(i) NaHMDS, THF, -20 °C (75 %); (ii) $LiAlH_4$, THF (91 %); (iii) H_2NNH_2, $CuSO_4$, $NaIO_4$, CH_3COOH, iPrOH (75 %); (iv) PCC, CH_2Cl_2 (95 %)

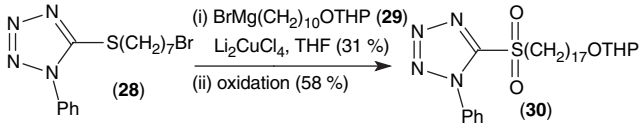
Scheme 7.



(i) LiHMDS, THF (78 %); (ii) $KO_2CN{=}NCO_2K$, AcOH, thf, MeOH (86 %); (iii) HIO_4 (97 %); (iv) NaOMe, MeOH, THF (70 %)

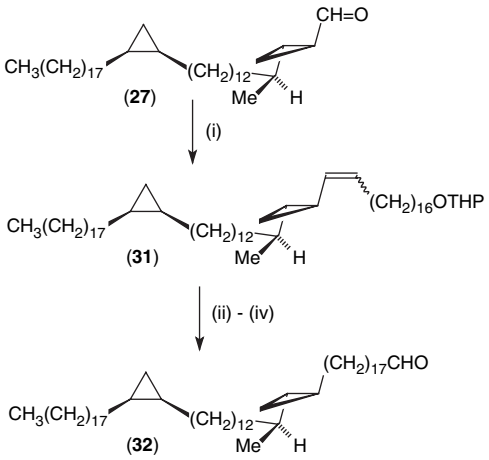
Scheme 8.

Finally, compound **27** was homologated at the aldehyde position to produce a C_{18}-chain. To achieve this, the difunctional species **30** was prepared by copper-catalysed coupling of the bromide **28** derived from 7-bromoheptanol, with the Grignard reagent **29**, followed by oxidation (Scheme 9).



Scheme 9.

The aldehyde **27** was coupled with the sulfone **30** in a Julia–Kocienski reaction.[23b] Deprotection of the THP ether **31** then saturation of the alkene using diimide, followed by oxidation gave the desired mycolaldehyde **32**, $[\alpha]_D^{22}$ +2.8 (*c* 1.02, $CHCl_3$). The overall ^1H NMR pattern for the cyclopropane signals of **32** was visually essentially identical to that reported for a mixture of mycolic acid esters containing both *cis*- and α-methyl-*trans*-cyclopropanes.[3,8,10] The *cis*-cyclopropane showed single protons at δ −0.32 (dt, *J* 4.3, 5.3 Hz) and 0.57 (dt, *J* 4.3, 8.0 Hz) and two protons within a multiplet at 0.62–0.71. The *trans*-cyclopropane unit showed three single-hydrogen multiplets at δ 0.1–0.2 and one at 0.45 (Scheme 10).



(i) (**30**), LiHMDS, THF (90 %); (ii) pTsOH, MeOH (95 %); (iii) H_2NNH_2, $CuSO_4$, Me_2CHOH, AcOH, $NaIO_4$ (85 %); (iv) PCC, CH_2Cl_2 (81 %)

Scheme 10.

Irradiation at δ 0.65 partly decoupled each of the signals at 0.57 and −0.32 (for the *cis*-cyclopropane unit), but also that at 0.2 and the methyl doublet at δ 0.9 (for the methyl adjacent to the *trans*-cyclopropane); it did not affect the signal at 0.45. The signal at δ 0.45 was coupled to each of those at 0.1–0.2 but not to the α-methyl-group signal at δ 0.9 (d, *J* 7.0 Hz). The signal for H_c is therefore part of the multiplet at 0.65 as previously identified on a natural sample, while those at δ 0.2 and 0.45, respectively, are assigned to H_b and H_a (Fig. 2) in contrast to an earlier assignment.[10] Moreover, the chemical shifts of the carbon signals for the two cyclopropanes and the adjacent CHMe group of the synthetic compound **32** were in very close agreement with those determined by Watanabe et al.;[10] thus the natural material gave signals at δ 18.6, 26.1 for the *trans*-cyclopropane CH-carbons, at 15.8 for the *cis*-cyclopropane CH-carbons and at 38.1 and 19.8 for the carbons of the CHMe fragment; the synthetic material showed corresponding signals at δ 18.62, 26.15, 15.79, 38.11 and 19.67. This close correspondence suggests that, even though the absolute stereochemistry of the natural material is still uncertain, the relative stereochemistry of the α-methyl-group and the cyclopropane is as in **32**.

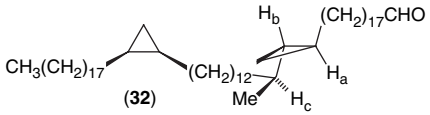


Figure 2.

Moreover, using **16** or its enantiomer,[14] and stereoisomers of intermediates related to **10**,[14,20] and the chemistry described above, it is expected that any absolute stereochemistry of mycolic acid containing an α-methyl-*trans*-cyclopropane unit may be synthesised.

2. Experimental

2.1. General

Unless stated, reagents were obtained from commercial suppliers. Solvents which had to be dry (e.g., ether, tetrahydrofuran) were dried over sodium wire. Boiling point of petroleum was 40–60 °C. Reactions under inert conditions were carried out under a slow stream of nitrogen from a balloon and septum. Those carried out at low temperatures were cooled using methylated spirit and liquid nitrogen. Silica gel (Merck 7736 silica gel) and silica plates used for thin layer and column chromatography were obtained from Aldrich. GLC was carried out on a Perkin–Elmer 8410 on a capillary column (15 m×0.53 mm). IR spectra were carried out on a Perkin–Elmer 1600 FTIR spectrometer from liquid films. ^{1}H NMR spectra were recorded on a Bruker AC250 or Advance 500 spectrometers. DEPT ^{13}C-spectra as reported are + for CH_2, − for CH or CH_3, dot for quaternary C. $[\alpha]_D$ values were recorded in $CHCl_3$ on a POLAAR 2001 Optical Activity polarimeter.

2.1.1. [(1*S*,2*R*)-2-((*S*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]methanol (9). Tetra-*n*-butylammonium fluoride (73 ml, 73 mmol) was added to a stirred solution of *tert*-butyl-[(1*S*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl-methyl]diphenylsilane (**8**)[20] (23 g, 56 mmol) in dry tetrahydrofuran (100 ml), at 0 °C under nitrogen. The mixture was allowed to reach room temperature and stirred for 16 h, when TLC showed no starting material was left, then cooled to 5 °C and quenched with satd aq ammonium chloride (50 ml) and the product was extracted with ethyl acetate (3×150 ml). The combined organic layers were washed with brine (100 ml), water (100 ml), dried and evaporated to give an oil. Chromatography (1:1 petroleum/ethyl acetate) gave *[(1S,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]methanol* (**9**) as a colourless oil (8.2 g, 85%) [Found M−H$^+$: 171.1023, $C_9H_{15}O$ requires: 171.1021], $[\alpha]_D^{22}$ −19.2 (*c* 1.24, $CHCl_3$), which showed δ_H (250 MHz, $CDCl_3$): 4.13 (1H, dd, *J* 5.5, 7.6 Hz), 3.85–3.77 (2H, m), 3.69 (1H, t, *J* 8 Hz), 3.43 (1H, dd, *J* 8.5, 11.3 Hz), 2.00 (1H, br s), 1.43 (3H, s), 1.34 (3H, s), 1.27–1.15 (1H, m), 1.03 (1H, br dq, *J* 5.5, 8.25 Hz), 0.89 (1H, br dt *J* 3.4, 6.1 Hz), 0.44 (1H, br q, *J* 5.5 Hz); δ_C (62.5 MHz, $CDCl_3$): 109.23, 77.47, 70.4, 63.24, 54.13, 27.6, 27.24, 18.5, 18.1, 8.8; ν_{max}: 3436, 2984, 2934 cm^{-1}.

2.1.2. (1*S*,2*R*)-2-((*S*)-2,2-Dimethyl-[1,3]dioxolan-4-yl) cyclopropanecarbaldehyde (10). Alcohol **9** (8.00 g, 46.5 mmol) in dichloromethane (25 ml) was added to a stirred suspension of pyridinium chlorochromate (20.05 g, 93 mmol) in dichloromethane (300 ml). The mixture was stirred vigorously for 2 h, when TLC showed no starting material, then poured into diethyl ether (500 ml), filtered through a pad of silica and washed well with ether. The filtrate was evaporated to give a yellow oil; chromatography (1:1 petroleum/ethyl acetate) gave an oil, *(1S,2R)-2-((S)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropanecarbaldehyde* (**10**) (6.9 g, 85%) [Found M−H$^+$: 169.0854; $C_9H_{13}O_3$ requires: 169.0854], $[\alpha]_D^{22}$ +36.1 (*c* 1.19, $CHCl_3$), which showed δ_H (250 MHz, $CDCl_3$): 9.41 (1H, d, *J* 5.2 Hz), 4.12 (1H, br t, *J* 6.1 Hz), 4.00 (1H, dd, *J* 6.1, 8 Hz), 3.66 (1H, br t, *J* 7.3 Hz), 2.02–1.95 (1H, m), 1.60 (1H, br t, *J* 7.3 Hz), 1.49–1.44 (1H, m), 1.42 (3H, s), 1.40–1.34 (1H, m), 1.33 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 200.68, 109.55, 74.5, 69.4, 27.2, 26.7, 25.8, 25.6, 12.77; ν_{max}: 1702, 1370, 1063 cm^{-1}.

2.1.3. (*E*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]acrylic acid methyl ester (11). Methyl (triphenylphosphoranylidene)acetate (14.23 g, 42 mmol) was added in portions to a stirred solution of aldehyde **10** (6.5 g, 38.2 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 refluxed with 1:1 petroleum/ether (50 ml) for 10 min. The precipitate was washed with petroleum/ether (30 ml). The solvent was evaporated and the residue was chromatographed (5:2 petroleum/ethyl acetate) to give *(E)-3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]acrylic acid methyl ester* (**11**) as a colourless oil (7.00 g, 81%) [Found M$^+$: 226.1200; $C_{12}H_{18}O_4$ requires: 226.1205], which showed δ_H (500 MHz, $CDCl_3$): 6.64 (1H, dd, *J* 10.4, 15.5 Hz), 5.95 (1H, d, *J* 15.5 Hz), 4.03 (1H, dd, *J* 6, 8.2 Hz), 3.83–3.78 (1H, m), 3.73 (3H, s), 3.64 (1H, br t, *J* 8.2 Hz), 1.79–1.73 (1H, m), 1.45 (3H, s), 1.41–1.37 (1H, m), 1.36 (3H, s), 1.30 (1H, dt, *J* 5.1, 8.2 Hz), 0.94 (1H, br q, *J* 5.4 Hz); δ_C (62.5 MHz, $CDCl_3$): 166.64, 148.88 (−), 120.97 (−), 109.17, 76.86 (−), 69.28 (+), 51.42 (−), 26.78 (−), 25.78 (−), 23.46 (−), 18.6(−), 13.79 (+); ν_{max}: 1701, 1643 cm^{-1}. There was less than 5% of the *Z*-isomer present. When methanol was used as a solvent, a 2:1 mixture of *E* and *Z*-isomers was obtained.

2.1.4. (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]butyric acid methyl ester (12). Methyl magnesium bromide (28.8 ml, 86.3 mmol) was added dropwise to a stirred suspension of copper bromide (6.2 g, 43 mmol) in dry tetrahydrofuran (100 ml) at −40 °C under nitrogen. The mixture was stirred for 30 min, then (*E*)-ester **11** (6.5 g, 28.7 mmol) in dry tetrahydrofuran (25 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 with satd aq ammonium chloride (30 ml) at −30 °C. The product was extracted with ethyl acetate (3×100 ml). The combined organic layers were washed with brine (50 ml), dried and evaporated to give a brown oil. Chromatography (5:2 petroleum/ethyl acetate) gave a colourless oil, *(S)-3-[(1R,2R)-2-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-cyclopropyl]butyric acid methyl ester* (**12**) (5.00 g, 72%) [Found M$^+$: 242.1528; $C_{13}H_{22}O_4$ requires: 242.1518], $[\alpha]_D^{22}$ +11.65 (*c* 1.3, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.09 (1H, dd, *J* 6, 7.6 Hz), 3.76 (1H, ddd, *J* 6.3, 7.85, 14 Hz), 3.68–3.65 (4H, including a singlet for the methoxy group), 2.33 (1H, dd, *J* 3.8, 14.8 Hz), 2.20 (1H, dd, *J* 9.8, 14.85 Hz), 1.52–1.59 (1H, m), 1.44 (3H, s), 1.35 (3H, s), 1.06 (3H, d, *J* 6.6 Hz), 0.94 (1H, dq, *J* 5.35, 8.2 Hz), 0.86 (1H, dt, *J* 4.7, 8.8 Hz), 0.77–0.71 (1H, m), 0.32 (1H, br q, *J* 5.32 Hz); δ_C (125 MHz, $CDCl_3$): 173.1, 108.74, 77.5, 70.2, 51.73, 42, 31.1, 27.1, 25.98, 23.3, 20.75, 19.6, 9.5; ν_{max}: 2984, 1737, 1061 cm^{-1}. There was less than ca. 6% of another isomer present. When a mixture of (2:1 *E*/*Z*) was used the same product was obtained.

2.1.5. (S)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)cyclopropyl]-butan-1-ol (13). Methyl ester **12** (4.2 g,

17.3 mmol) in dry tetrahydrofuran (15 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.32 g, 34.7 mmol) in tetrahydrofuran (50 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 decahydrate (20 ml) until a white solid formed. The precipitate was filtered off and washed with tetrahydrofuran (2×20 ml). The filtrate was evaporated to give a crude product; chromatography (1:1 petroleum/ethyl acetate) gave *(S)-3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]-butan-1-ol* (**13**) as a colourless oil (3.26 g, 88%) [Found M^+-CH_3: 199.1344; $C_{11}H_{19}O_3$ requires: 199.1334], $[\alpha]_D^{22}$ −8.9 (*c* 1.53, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 4.19 (1H, dd, *J* 5.65, 7.55 Hz), 3.88 (1H, dt, *J* 6, 7.86 Hz), 3.71 (2H, t, *J* 7.9 Hz), 3.67–3.62 (1H, br m), 1.75 (1H, br s), 1.67–1.59 (2H, m), 1.53–1.46 (1H, m), 1.45 (3H, s), 1.36 (3H, s), 1.04 (3H, d, *J* 6.6 Hz), 0.95 (1H, dq, *J* 5.65, 8.5 Hz), 0.85 (1H, dt, *J* 4.4, 8.5 Hz), 0.74–0.68 (1H, m), 0.28 (1H, br q, *J* 5.65 Hz); δ_C (125 MHz, $CDCl_3$): 108.5, 77.1, 70.1, 60.6, 40.3, 29.64, 26.78, 25.7, 23.87, 20.35, 19.1, 8.3; ν_{max}: 3432, 2983 cm^{-1}.

2.1.6. 3,5-Dinitrobenzoic acid (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyl ester. 3,5-Dinitrobenzoyl chloride (0.42 g, 1.82 mmol), was added to a stirred solution of (*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butan-1-ol (**13**) (0.3 g, 1.4 mmol) and pyridine (1.5 ml) in toluene (5 ml) at room temperature. The mixture was refluxed for 4 h then cooled to room temperature and the solvent was evaporated. The residue was treated with water (10 ml) and extracted with ether (3×20 ml). The combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil; chromatography (1:1 petroleum/ether) gave a white solid, *3,5-dinitrobenzoic acid (S)-3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]dioxolan-4-yl)cyclopropyl]butyl ester* (0.32 g, 56%), mp 77–79 °C [Found C, 56.0, H, 5.8, N, 6.9; $C_{19}H_{24}O_8N_2$ requires: C, 55.88, H, 5.92, N, 6.85], $[\alpha]_D^{22}$ −26 (*c* 0.4, $CHCl_3$), which showed δ_H (250 MHz, $CDCl_3$): 9.23 (1H, br t, *J* 2.1 Hz), 9.14 (2H, br d, *J* 2.1 Hz), 4.56–4.42 (2H, m), 4.18–4.08 (1H, m), 3.81–3.68 (2H, m), 2.10–1.88 (1H, m), 1.81–1.67 (1H, m), 1.42 (3H, s), 1.38–1.29 (1H, m), 1.28 (3H, s), 1.13 (3H, d, *J* 6.4 Hz), 1.08–0.79 (3H, m), 0.33 (1H, br q, *J* 5 Hz); δ_C (62.5 MHz, $CDCl_3$): 162.5, 148.7, 133.8, 129.3, 122.38, 108.56, 70.1, 65.2, 33.8, 30.4, 28.75, 25.7, 23.5, 20.03, 19.1, 8.73; ν_{max}: 2923, 2853, 1732, 1544 cm^{-1}.

2.1.7. Crystal structure determination for the 3,5-dinitrobenzoate of (13). *Crystal data*: $C_{19}H_{24}N_2O_8$, M=408.4, orthorhombic, space group $P2_12_12_1$, a=5.6009(3), b=16.6472(8), c=21.3374(10) Å, V=1989.48(17) $Å^3$, Z=4, D_c=1.364 g cm^{-3}, μ=0.11 mm^{-1} (Mo Kα, λ=0.71073 Å), T=150 K. Of 14,574 reflections measured on a Bruker AXS SMART CCD diffractometer, 2057 were unique (θ<25°, R_{int}=0.038). The structure was solved by standard direct methods and refined on F^2 values; H atoms were constrained with a riding model. In the absence of significant anomalous scattering, Friedel pairs were merged, and the absolute configuration was assigned on the basis of the known configuration of compound **8**. R=0.033 (F values, $F^2>2s$), R_w=0.079 (F^2 values, all data), goodness-of-fit=1.125 for 266 refined parameters, final difference map within ±0.27 $eÅ^{-3}$. Software: Bruker SMART, SAINT and SHELXTL. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCD283460. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

2.1.8. 2-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butylsulfanyl}benzothiazole (14). Diethyl azodicarboxylate (2.56 g, 14.7 mmol) in dry tetrahydrofuran (5 ml) was added to a stirred solution of alcohol **13** (3 g, 14.0 mmol), triphenylphosphine (4.04 g, 15 mmol) and 2-mercaptobenzthiazole (2.46 g, 14.7 mmol) in tetrahydrofuran (20 ml) at 5 °C under nitrogen. The mixture was allowed to reach room temperature, stirred for 24 h, then the solvent was evaporated. The residue was dissolved in ethyl acetate (50 ml) and petroleum (50 ml), stirred for 15 min, filtered through Celite and evaporated to give a yellow oil. This was dissolved in ether, suspended on silica and then columned (1:1 petroleum/ether) to give *2-{(S)-3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]butylsulfanyl}benzothiazole* (**14**) as a pale yellow oil (4.5 g, 89%) [Found M^+: 363.1317; $C_{19}H_{25}O_2S_2N$ requires: 363.1327], $[\alpha]_D^{22}$ −45.05 (*c* 1.485, $CHCl_3$), which showed δ_H (250 MHz, $CDCl_3$): 7.88 (1H, br dd, *J* 0.9, 7.6 Hz), 7.76 (1H, br dd, *J* 0.9, 8 Hz), 7.42 (1H br dt, *J* 1.2, 7.3 Hz), 7.27 (1H, br dt, *J* 1.2, 8 Hz), 4.09 (1H, dd, *J* 5.8, 7.6 Hz), 3.76 (1H, br dt, *J* 5.8, 8.25 Hz), 3.63 (1H, br t, *J* 7.6 Hz), 3.52–3.24 (2H, m), 1.95–1.83 (1H, m), 1.81–1.65 (1H, m), 1.43 (3H, s), 1.33 (3H, s), 1.29–1.19 (1H, m), 1.10 (3H, d, *J* 6.4 Hz), 1.04–0.71 (4H, m), 0.31 (1H, br q, *J* 6.4 Hz); δ_C (62.5 MHz, $CDCl_3$): 166.6, 153.2, 135.1, 126.1, 124.2, 121.5, 120.9, 108.3, 77.2, 70, 36.7, 32.65, 31.1, 26.8, 25.6, 23.5, 19.6, 19.4, 8.9; ν_{max}: 3062, 2982, 1461, 1427, 1060 cm^{-1}.

2.1.9. 2-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-Dimethyl[1,3]dioxolan-4-yl)cyclopropyl]-butane-1-sulfonyl}benzothiazole (15). A solution of ammonium heptamolybdate(VI) tetrahydrate (1.34 g, 1.1 mmol), in 35% H_2O_2 (w/w) (5.3 ml, 54.4 mmol) was added dropwise at 5 °C to a stirred solution of compound **14** (4.2 g, 11.5 mmol) in methylated spirit (100 ml). The resulting yellow solution was stirred for 1 h at this temperature and then for 16 h at room temperature. The solvent was evaporated to give a yellow solid which was treated with water (50 ml) and extracted with dichloromethane (3×50 ml); the combined organic layers were washed with brine (50 ml), dried and evaporated to give the crude product. This was purified by chromatography (1:1 petroleum/ethyl acetate) to give *2-{(S)-3-[(1R,2R)-2-((S)-2,2-dimethyl[1,3]-dioxolan-4-yl)cyclopropyl]-butane-1-sulfonyl}benzothiazole* as a thick yellow oil (**15**) (3.08 g, 67.4%) [Found M^+: 395.123; $C_{19}H_{25}O_4S_2N$ requires: 395.1225], $[\alpha]_D^{22}$ −34.1 (*c* 1.36, $CHCl_3$), which showed δ_H (250 MHz, $CDCl_3$): 8.23 (1H, br d, *J* 8.2 Hz), 8.04 (1H, br d, *J* 8 Hz), 7.66 (1H, dt, *J* 1, 7.3 Hz), 7.61 (1H, dt, *J* 1, 8.2 Hz), 4.04 (1H, dd, *J* 6, 7.9 Hz), 3.76 (1H, br q, *J* 7.6 Hz), 3.63–3.56 (2H, m), 3.54–3.48 (1H, m), 2.03–1.96 (1H, m), 1.81–1.73 (1H, m), 1.41 (3H, s), 1.37–1.33 (1H, m), 1.31 (3H, s), 1.06 (3H, d, *J* 6.4 Hz), 0.99–0.92 (1H, dt,

J 5.4, 8.5 Hz), 0.84 (1H, br dt, *J* 4, 8.8 Hz), 0.72–0.65 (1H, m), 0.31 (1H, br q, *J* 5.4 Hz); δ_C (62.5 MHz, $CDCl_3$): 165.9, 152.6, 136.6, 128.1, 127.8, 125.4, 122.4, 76.5, 70, 52.5, 32.3, 29.2, 26.77, 25.65, 23.1, 19.6, 19.3, 8.46; ν_{max}: 2982, 1735, 1472, 1059 cm^{-1}. The second product was (*S*)-1-{(1*R*,2*R*)-2-[(*S*)-3-(benzothiazole-2-sulfonyl)-1-methylpropyl]cyclopropyl}ethane-1,2-diol (0.84 g, 20.45%) which was reprotected with 2,2-dimethoxypropane in dichloromethane in the presence of a catalytic amount of PTSA at room temperature in 95% yield.

2.1.10. Butyric acid (1*R*,2*S*)-2-(benzothiazole-2-sulfonylmethyl)cyclopropylmethyl ester (18). Diethyl azodicarboxylate (18.1 g, 103.7 mmol) in dry tetrahydrofuran (50 ml) was added to a stirred solution of *cis*-(1*R*,2*S*)-1-butyryloxymethyl-2-hydroxymethylcyclopropane (**16**) (17 g, 98.8 mmol),[22] triphenylphosphine (28.5 g, 108.72 mmol) and 2-mercaptobenzthiazole (17.35 g, 103.7 mmol) in dry tetrahydrofuran (200 ml) at 0 °C. The mixture was allowed to reach room temperature and stirred for 18 h. The solvent was evaporated and the residue was treated with petroleum/ether (5:2) (200 ml) and the precipitate was filtered off on a sinter. The filter cake was washed with petroleum/ether. The combined organic layers were evaporated to give a pale yellow oil, which was columned (5:2 petroleum/ethyl acetate) to give *butyric acid (1R,2S)-2-(benzothiazol-2-ylsulfanylmethyl)cyclopropylmethyl ester* (**17**) as a thick yellow oil (23.5 g, 73%); $[\alpha]_D^{22}$ −4.3 (*c* 1.48, $CHCl_3$) (lit. value (1*S*,2*R*)-isomer $[\alpha]_D^{22}$ +4.9 (*c* 2.4, $CHCl_3$);[14] [Found M^+: 321.083; $C_{16}H_{19}O_2S_2N$ requires: 321.086], which showed δ_H (250 MHz, $CDCl_3$): 7.83 (1H, br d, *J* 8.04 Hz), 7.72 (1H, br d, *J* 8.4 Hz), 7.46–7.33 (1H, m), 7.27–7.22 (1H, m), 4.32 (1H, dd, *J* 6.5, 12 Hz), 3.98 (1H, dd, *J* 8.5, 12 Hz), 3.52 (1H, dd, *J* 7.5, 13.27 Hz), 3.34 (1H, dd, *J* 7.4, 13.27 Hz), 2.34 (2H, t, *J* 7.3 Hz), 1.65 (2H, sext, *J* 5.3 Hz), 1.45–1.32 (2H, m), 0.93 (3H, t, *J* 7.3 Hz), 0.95–0.85 (1H, m), 0.37 (1H, br q, *J* 5.6 Hz); δ_C (62.5 MHz, $CDCl_3$): 173.7, 166.76, 153.2, 135.2, 126.00, 124.2, 121.4, 121, 64.1, 36.2, 33.9, 18.4, 16.13, 15.7, 13.7, 11.00; ν_{max}: 1733, 1458, 1427, 1180 cm^{-1}.

A solution of ammonium heptamolybdate(VI) tetra-hydrate (6.15 g, 4.9 mmol) in 35% H_2O_2 (w/w) (23.2 ml, 238 mmol) at 5 °C was added to a stirred solution of the above ester (17 g, 53 mmol) in methylated spirit (150 ml). The resulting yellow solution was stirred for 1 h at this temperature then for 16 h at room temperature. The solvent was evaporated to give a yellow solid, which was diluted with water (100 ml) and extracted with dichloromethane (3×100 ml). The combined organic layers were washed with brine (50 ml), dried and evaporated to give an oil. Chromatography (5:3 petroleum/ethyl acetate) gave butyric acid (1*R*,2*S*)-2-(benzothiazole-2-sulfonylmethyl)cyclopropylmethyl ester (**18**) as a thick yellow oil (17.3 g, 92%), which showed δ_H (250 MHz, $CDCl_3$): 8.21–8.15 (1H, m), 7.99–7.95 (1H, m), 7.62–7.45 (2H, m), 4.24 (1H, distorted dd, *J* 6, 12 Hz), 3.83–3.72 (2H, m), 3.35 (1H, distorted dd, *J* 9.5, 14.7 Hz), 2.22 (2H, t, *J* 7.4 Hz), 1.65 (2H, sext, *J* 7.4 Hz), 1.38–1.30 (2H, m), 0.95–0.80 (4H, m, including a triplet, *J* 7.36 Hz), 0.28 (1H, br q, *J* 5.7 Hz); δ_C (62.5 MHz, $CDCl_3$): 173.4, 165.8, 152.6, 136.8, 128, 127.6, 125.4, 122.3, 63.6, 55.1, 36, 18.35, 14.4, 13.6, 9.7, 9.1; ν_{max}: 1730, 1707, 1470, 762 cm^{-1}. $[\alpha]_D^{22}$ +56.1 (*c* 1.13, $CHCl_3$) (lit. value (1*S*,2*R*)-isomer $[\alpha]_D^{22}$ −58.3 (*c* 1.59, $CHCl_3$)[14]; *m/z*: M^+ (353), 266 ($M^+-C_4H_7O_2$), 155 ($M^+-C_7H_4S_2O_2N$).

2.1.11. Heptadecan-1-ol. 1-Bromoheptane (34 g, 189.8 mmol) in dry tetrahydrofuran (50 ml) was added dropwise to a suspension of magnesium turnings (5.96 g, 246.8 mmol) in dry tetrahydrofuran (80 ml) at a rate sufficient to maintain a steady reflux. Once the exothermic reaction had subsided, the mixture was refluxed for 1 h. The Grignard reagent was cooled to −10 °C, then 10-bromodecanol (15 g, 63.3 mmol) in tetrahydrofuran (50 ml) was added. The mixture was cooled to −40 °C followed by the addition of dilithium tetrachlorocuprate (5 ml) then stirred for 2 h at −40 °C and at room temperature for 12 h. Satd aq ammonium chloride (100 ml) was added together with ethyl acetate (100 ml). The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (2×50 ml). The combined organic layers were washed with water, dried and evaporated to give a residue, which was columned (5:1 petroleum/ethyl acetate) to give heptadecan-1-ol as a white solid (14.5 g, 89.5%), mp 54–56 °C [Found M^+: 256.2777; $C_{17}H_{36}O$ requires: 256.2766], which showed δ_H (250 MHz, $CDCl_3$): 3.65 (2H, t, *J* 6.4 Hz), 1.62–1.27 (31H, m), 0.89 (3H, t, *J* 7 Hz); δ_C (62.5 MHz, $CDCl_3$): 62.9, 32.7, 31.92, 29.7 (v. broad), 29.45, 29.36, 25.7, 22.67, 14.1; ν_{max}: 3430 cm^{-1}.

2.1.12. Heptadecanal. Heptadecan-1-ol (15.0 g, 58 mmol) in dichloromethane (50 ml) was added at room temperature to a stirred suspension of pyridinium chlorochromate (25.2 g, 117 mmol) in dichloromethane (250 ml). A black colour appeared after 10 min. The mixture was stirred for 2 h, when TLC showed no starting material, then diluted with ether (500 ml) and filtered through a pad of silica. The solvent was evaporated to give a residue, which was purified by chromatography (5:1 petroleum/ether) to give heptadecanal as a white solid (13.6 g, 91%), mp 45–47 °C [Found M^+: 254.2614; $C_{17}H_{34}O$ requires: 254.2610], which showed δ_H (250 MHz, $CDCl_3$): 9.73 (1H, t, *J* 1.8 Hz), 2.43 (2H, dt, *J* 1.8, 7.3 Hz), 1.72–1.62 (2H, m), 1.43–1.21 (26H, m), 0.91 (3H, t, *J* 7 Hz); δ_C (62.5 MHz, $CDCl_3$): 202.89, 43.89, 33.98, 31.9, 29.68, 29.65, 29.63, 29.57, 29.42, 29.35, 29.23, 29.16, 29.06, 24.68, 22.67, 22.07, 14.07; ν_{max}: 1727 cm^{-1}.

2.1.13. ((1*R*,2*S*)-2-Octadecycyclopropyl)methanol (21). Sodium hexamethyldisilazide (62 ml, 62 mmol, 1 M) was added to a stirred solution of butyric acid (1*R*,2*S*)-2-(benzothiazole-2-sulfonylmethyl)cyclopropylmethyl ester (**18**) (16.8 g, 47.6 mmol) and heptadecanal (11 g, 43.3 mmol) in dry tetrahydrofuran (100 ml) under nitrogen at −20 °C. The mixture was stirred for 2 h at this temperature, then allowed to reach room temperature for 12 h. This was quenched with water (20 ml) at 0 °C, then diluted with ether (100 ml). The organic layer was separated and the aqueous layer was extracted with ether (2×50 ml). The combined organic layers were dried and evaporated to give a pale yellow oil, which was columned (20:1 petroleum/ether) to give 1.3:1 *(E/Z)-butyric acid (1R,2R)-2-octadec-1-enylcyclopropylmethyl ester* (**19**) (10.5 g, 68%). The (*E*/*Z*) mixture (8 g, 20.4 mmol) in tetrahydrofuran (50 ml) was added dropwise over 15 min to a suspension of lithium aluminium hydride (1.55 g, 40.8 mmol) in tetrahydrofuran (150 ml) at room temperature. The mixture was refluxed for 1 h, then cooled

to room temperature and quenched carefully with freshly prepared satd aq sodium sulfate decahydrate (40 ml) until a white precipitate formed, followed by the addition of magnesium sulfate (10 g). The mixture was stirred vigorously for 10 min, filtered through a pad of Celite and washed well with tetrahydrofuran (2×50 ml). The combined organic layers were dried and evaporated to give 1.3:1 *(E/Z)-((1R,2R)-2-octadec-1-enylcyclopropyl)methanol* (**20**) (5.4 g, 84.3%), which was used for the next step without purification.

Sodium metaperiodate (36.55 g, 170.8 mmol) in hot water (100 ml) was added over a 90 min at 70–80 °C to a stirred solution of alcohol **20** (5.5 g, 17 mmol) in isopropyl alcohol (100 ml), acetic acid (2 ml), satd aq copper sulfate (2 ml) and hydrazine hydrate (15 ml). The mixture was stirred for another 2 h to reach room temperature, then diluted with ether (150 ml). The organic layer was separated and the aqueous layer was extracted with ether (2×50 ml). The combined organic layers were washed with water (2×50 ml), dried and evaporated. The crude product was purified by chromatography (5:1 petroleum/ether) to give *((1R,2S)-2-octadecylcyclopropyl)methanol* (**21**) as a white solid (4.5 g, 81%), mp 54–56 °C [Found: M^+-H_2O: 306.3289, $C_{22}H_{42}$ requires 306.3287], $[\alpha]_D^{22}$ +11.98 (*c* 1.06, $CHCl_3$), which showed δ_H (500 MHz): 3.66 (1H, ddd, *J* 1.25, 7.25, 11.35 Hz), 3.61 (1H, br ddd, *J* 0.95, 8.2, 11 Hz), 1.58 (1H, br s), 1.50–1.41 (2H, m), 1.37–1.22 (32H, m), 1.15–1.08 (1H, m), 0.91 (3H, t, *J* 7 Hz), 0.85 (1H, m), 0.73 (1H, ddt, *J* 0.9, 4.7, 9.75 Hz), 0.03 to −0.028 (1H, br q, *J* 4.4 Hz); δ_C (62.5 MHz, $CDCl_3$): 63.3, 31.9, 30.15, 29.68, 29.64, 29.56, 29.34, 28.54, 22.66, 18.12, 16.14, 14.08, 9.45; ν_{max}: 3352 cm^{-1}.

2.1.14. ((1*R*,2*S*)-2-Octadecylcyclopropanecarbaldehyde (22). Alcohol **21** (2.5 g, 7.7 mmol) in dichloromethane (15, ml) was added to a stirred suspension of pyridinium chlorochromate (3.34 g, 15 mmol) in dichloromethane (50 ml) at room temperature. The mixture was stirred vigorously for 3 h, when TLC showed no starting material, poured into diethyl ether (200 ml) and filtered on a pad of silica then washed well with ether. The filtrate was evaporated to give a white solid; chromatography (5:2 petroleum/ether) gave *((1R,2S)-2-octadecylcyclopropanecarbaldehyde* (**22**) as a white solid (2.1 g, 84.5%), mp 39–41 °C [Found M^+: 322.3232; $C_{22}H_{42}O$ requires: 322.3236], $[\alpha]_D^{22}$ +7.62 (*c* 1.455, $CHCl_3$), which showed δ_H (250 MHz, $CDCl_3$): 9.35 (1H, d, *J* 5.5 Hz), 1.92–1.81 (1H, m), 1.65–1.23 (37H, m), 0.88 (3H, t, *J* 7 Hz); ν_{max} 1695 cm^{-1}.

2.1.15. 10-((1*R*,2*S*)-2-Octadecylcyclopropyl)decan-1-ol. Sodium hexamethyldisilazide (8.1 ml, 8.1 mmol) was added to a stirred solution of 2,2-dimethylpropionic acid 9-(benzothiazole-2-sulfonyl)nonyl ester (**23**) (2.85 g, 6.7 mmol) and aldehyde (**22**) (1.8 g, 5.6 mmol) in dry tetrahydrofuran (30 ml) under nitrogen at −10 °C. After 1 h at this temperature, it was allowed to reach room temperature for 12 h, then cooled to 0 °C, quenched with satd aq ammonium chloride (20 ml), then diluted with ether (100 ml). The organic layer was separated and the aqueous layer was extracted with ether (2×30 ml). The combined organic layers were dried and evaporated to give a pale yellow oil; chromatography (5:1 petroleum/ether) gave a yellow oil, *2,2-dimethylpropionic acid 10-((1R,2S)-2-octadecylcyclopropyl)dec-9-enyl ester* as a 1.3:1 (*E/Z*) mixture (2.24 g, 75%).

The above mixture (2.1 g, 3.9 mmol) in tetrahydrofuran (15 ml) was added dropwise over 5 min to a suspension of lithium aluminium hydride (0.3 g, 7.9 mmol) in tetrahydrofuran (20 ml) at room temperature. The mixture was refluxed for 1 h, then allowed to reach room temperature and quenched carefully with freshly prepared satd aq sodium sulfate decahydrate (10 ml) until a white precipitate was formed, followed by the addition of magnesium sulfate (10 g). The mixture was stirred vigorously for 10 min then filtered through a pad of Celite and washed well with tetrahydrofuran (2×25 ml). The combined organic layers were dried and evaporated to give *(E/Z)-10-((1R,2S)-2-octadecylcyclopropyl)dec-9-en-1-ol* as a colourless oil (1.6 g, 91%), which was used for the next step without purification.

Sodium metaperiodate (7.64 g, 35.7 mmol) in hot water (50 ml) was added over 1 h at 70–80 °C to a stirred solution of (*E/Z*)-10-((1*R*,2*S*)-2-octadecylcyclopropyl)dec-9-en-1-ol (1.6 g, 3.57 mmol) in isopropyl alcohol (50 ml), acetic acid (1 ml), satd aq copper sulfate (1 ml) and hydrazine hydrate (10 ml). The mixture was stirred for 2 h to reach room temperature, then diluted with ether (100 ml). The organic aqueous layer was extracted with ether (2×50 ml). The combined organic layers were washed with water (2×50 ml), dried and evaporated to give a solid; recrystallisation from petroleum gave *10-((1R,2S)-2-octadecylcyclopropyl)decan-1-ol* as a white solid (1.2 g, 75%), mp 58–60 °C [Found M^+: 450.4795, $C_{31}H_{62}O$ requires: 450.4801], $[\alpha]_D^{22}$ +0.54 (*c* 0.735, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 3.66 (2H, t, *J* 6.65 Hz), 1.61 (2H, pen, *J* 6.65 Hz), 1.53 (1H, br s), 1.45–1.27 (48H, m), 1.18–1.12 (2H, m), 0.91 (3H, t, *J* 7 Hz), 0.68–0.63 (2H, m), 0.59 (1H, dt, *J* 4.1, 8.2 Hz), −0.31 (1H, br q, *J* 5.35 Hz); δ_C (62.5 MHz, $CDCl_3$): 63.11, 32.83, 31.92, 30.21, 29.7 (v. broad), 29.66, 29.61, 29.6, 29.44, 29.35, 28.72, 25.74, 22.68, 15.79, 14.1, 10.92; ν_{max}: 3352 cm^{-1}.

2.1.16. 10-((1*R*,2*S*)-2-Octadecyl-cyclopropyl)decanal (24). 10-((1*R*,2*S*)-2-Octadecylcyclopropyl)decan-1-ol (1.00 g, 2.2 mmol) in dichloromethane (10 ml) was added to a refluxing stirred suspension of pyridinium chlorochromate (1.2 g, 5.5 mmol) in dichloromethane (20 ml). The mixture was stirred vigorously for 2 h, when TLC showed no starting material. The mixture was cooled to room temperature and poured into ether (100 ml) and the precipitate filtered on a pad of silica and washed well with ether. The filtrate was evaporated to give a white solid; chromatography (5:1 petroleum/ether) gave *10-((1R,2S)-2-octadecyl-cyclopropyl) decanal* (**24**) as a white solid (0.95 g, 95%), mp 48–50 °C [Found M^+: 448.4647; $C_{31}H_{60}O$ requires: 448.4644], $[\alpha]_D^{24}$ +0.17 (*c* 1.18, $CHCl_3$), which showed δ_H (500 MHz, $CDCl_3$): 9.78 (1H, t, *J* 1.9 Hz), 2.43 (2H, dt, *J* 1.9, 7.6 Hz), 1.65 (2H, pen, *J* 7.5 Hz), 1.43–1.25 (46H, m), 1.19–1.12 (2H, m), 0.91 (3H, t, *J* 7 Hz), 0.69–0.65 (2H, m), 0.58 (1H, dt, *J* 4.1, 7.9 Hz), −0.31 (1H, br q, *J* 5.35 Hz); δ_C (125 MHz, $CDCl_3$): 202.77, 43.9, 31.9, 30.22, 30.2, 29.74, 29.7, 29.66, 29.62, 29.44, 29.36, 29.2, 28.72, 28.7, 22.68, 22.1, 15.78, 14.1, 10.9; ν_{max}: 1695 cm^{-1}.

2.1.17. 2, 2-Dimethylpropionic acid 9-hydroxynonyl ester. Trimethylacetyl chloride (22.57 g, 187 mmol) was added at room temperature to a stirred solution of 1,9-nonandiol (25 g, 155.9 mmol), pyridine (22.9 ml, 28 mmol) and

4-dimethylaminopyridine (0.5 g) in tetrahydrofuran (200 ml) at 10 °C. The reaction was allowed to reach room temperature and stirred for 16 h. A white precipitate was formed, and the mixture was diluted with ether (200 ml) and washed with dil hydrochloric acid (5%), then the organic layer was separated and the aqueous layer was re-extracted with ether (2×100 ml). The combined organic layers were washed with satd aq sodium bicarbonate (100 ml), water (100 ml), dried and evaporated to give a colourless oil. The crude product was columned, eluting with 5:1 petroleum/ethyl acetate, to give *2,2-dimethylpropionic acid 9-hydroxynonyl ester* as a colourless oil (18.83 g, 49%), [Found M^+: 244.2039; $C_{14}H_{28}O_3$ requires: 244.2038], which showed δ_H (250 MHz, $CDCl_3$): 4.4.03 (2H, t, *J* 6.73 Hz), 3.63 (2H, t, *J* 6.43 Hz), 2.04 (1H, br s), 1.62–1.57 (4H, m), 1.30 (10H, br s), 1.15 (9H, s), δ_C (62.5 MHz, $CDCl_3$): 178.7, 64.4, 62.3, 38.7, 32.7, 29.4, 29.3, 29.1, 28.5, 27.1, 25.8, 25.6; ν_{max}: 3440, 1729 cm^{-1}.

2.1.18. 2,2-Dimethylpropionic acid 9-(benzothiazol-2-ylsulfanyl)nonyl ester. Diethyl azodicarboxylate (11.24 g, 64.5 mmol) in dry tetrahydrofuran (25 ml) was added to a stirred solution of 2,2-dimethylpropionic acid 9-hydroxy-nonyl ester (15 g, 61.5 mmol), triphenylphosphine (17.73 g, 67.6 mmol) and 2-mercaptobenzthiazole (10.8 g, 64.5 mmol) in dry tetrahydrofuran (120 ml) at 0 °C, then allowed to reach room temperature and stirred for 18 h. The solvent was evaporated and the residue was treated with petroleum/ether (5:2) (200 ml) and the precipitate was filtered off on a sinter. The filter cake was washed with petroleum/ether. The combined organic layers were evaporated to give an oil; chromatography (5:1 petroleum/ether) gave *2,2-dimethylpropionic acid 9-(benzothiazol-2-ylsulfanyl)-nonyl ester* as a colourless oil (18 g, 75%) [Found M^+: 393.1790; $C_{21}H_{31}O_2S_2N$ requires: 393.1796], which showed δ_H (250 MHz, $CDCl_3$): 7.83 (1H, br d, *J* 8.04 Hz), 7.72 (1H, br d, *J* 8.4 Hz), 7.45–7.22 (2H, m), 4.00 (2H, t, *J* 6.4 Hz), 3.30 (2H, t, *J* 7 Hz), 1.82–1.74 (2H, pen, *J* 7 Hz), 1.58–1.54 (2H, m), 1.46–1.41 (2H, m), 1.28 (8H, br s), 1.15 (9H, s); δ_C (62.5 MHz, $CDCl_3$): 178.6, 167.35, 153.34, 135.1, 125.97, 124.1, 121.4, 120.9, 64.3, 33.6, 29.3, 29.1, 28.9, 28.7, 28.5, 27.2, 25.8, 15.2; ν_{max}: 1726 cm^{-1}.

2.1.19. 2,2-Dimethylpropionic acid 9-(benzothiazole-2-sulfonyl)nonyl ester (23). A solution of ammonium heptamolybdate(VI) tetra-hydrate (3.55 g, 2.8 mmol) in 35% H_2O_2 (w/w) (14 ml, 143.5 mmol) was added dropwise at 5 °C to a stirred solution of 2,2-dimethylpropionic acid 9-(benzothiazol-2-ylsulfanyl)nonyl ester (12 g, 30.5 mmol) in methylated spirit (200 ml). The resulting yellow solution was stirred for 1 h at this temperature then for 16 h at room temperature. The solvent was evaporated to give a yellow solid, which was diluted with water (100 ml) and the product was extracted with dichloromethane (3×100 ml). The combined organic layers were washed with brine (50 ml), dried and evaporated to give an oil. Chromatography (5:1 petroleum/ethyl acetate) gave *2,2-dimethylpropionic acid 9-(benzothiazole-2-sulfonyl)nonyl ester* (**23**) as a thick yellow oil (9.5 g, 73%) [Found M^+: 425.1711; $C_{21}H_{31}O_4S_2N$ requires: 425.1695], which showed δ_H (250 MHz, $CDCl_3$): 8.23 (1H, br d, *J* 8 Hz), 8.01 (1H, br d, *J* 8 Hz), 7.65–7.55 (2H, m), 4.02 (2H, t, *J* 6.7 Hz), 3.53–3.46 (2H, m), 1.92–1.82 (2H, m), 1.62–1.55 (2H, m), 1.45–1.35 (2H, m), 1.27 (8H, br s), 1.18 (9H, s); δ_C (62.5 MHz, $CDCl_3$): 178.62, 165.86, 152.7, 136.74, 127.99, 127.64, 125.4, 122.33, 64.3, 54.67, 38.7, 29, 28.8, 28.5, 28.16, 27.17, 25.78, 22.2; ν_{max}: 1723, 1148 cm^{-1}.

2.1.20. (*S*)-2,2-Dimethyl-4-{(1*R*,2*R*)-2-[(*S*)-1-methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]cyclopropyl}-[1,3]dioxolane (25). Lithium hexamethyldisilazide (2.8 ml, 2.8 mmol) was added dropwise to a stirred solution of 2-{(*S*)-3-[(1*R*,2*R*)-2-((*S*)-2,2-dimethyl[1,3]dioxolan-4-yl) cyclo-propyl]butane-1-sulfonyl}benzothiazole (**18**) (0.91 g, 2.3 mmol) and 10-((1*R*,2*S*)-2-octadecylcyclopropyl)-decanal (**24**) (0.9 g, 2 mmol) in dry tetrahydrofuran (20 ml) under nitrogen at −5 °C. The reaction was exothermic and the temperature rose to 0 °C, resulting in a dark orange solution. The mixture was allowed to reach room temperature and stirred for 16 h, cooled to 0 °C and quenched with satd aq ammonium chloride (5 ml). The product was extracted with 1:1 petroleum/ether (2×50 ml); the combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil. Chromatography (5:1 petroleum/ether) gave *(S)-2,2-dimethyl-4-{(1R,2R)-2-[(E/Z)-(S)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyl)tridec-3-enyl]-cyclopropyl}-[1,3]dioxolane* (**25**) (0.98 g, 78%). Freshly distilled acetic acid (1.37 g, 22.9 mmol) in methanol (5 ml) was added slowly to a stirred solution of the above [1,3]-dioxo-lane (0.9 g, 1.43 mmol) and dipotassium azodicarboxylate (2.78 g, 14.3 mmol) in methanol/tetrahydrofuran (30 ml) (2:1) at room temperature. The mixture was stirred for 24 h then additional dipotassium azodicarboxylate (2.78 g) and acetic acid (1.4 g) were added and stirred for a further 24 h. The reaction was poured into water (15 ml) slowly and the product was extracted with petroleum/ether (3×30 ml). The combined organic layers were washed with satd aq sodium bicarbonate (15 ml), dried and evaporated, to give a residue; chromatography (10:1 petroleum/ether) gave *(S)-2,2-dimethyl-4-{(1R,2R)-2-[(S)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyl)-tridecyl]cyclopropyl}[1,3]-dioxolane* as a colourless oil which solidified later (0.75 g, 86%) [Found M^+: 630.6300, $C_{43}H_{82}O_2$ requires: 630.6315], $[\alpha]_D^{24}$ −7.0 (*c* 1.1, $CHCl_3$); which showed δ_H (500 MHz, $CDCl_3$): 4.11–4.09 (1H, m), 3.72–3.68 (2H, m), 1.45 (3H, s), 1.42–1.13 (62H, br m, including a singlet integrating to 3H), 1.02 (3H, br s), 0.95–0.91 (1H, m), 0.88 (3H, t, *J* 7 Hz), 0.83 (1H, dt, *J* 4.5, 8 Hz), 0.71–0.64 (3H, m), 0.57 (1H, dt, *J* 4.5, 8.5 Hz), 0.24 (1H, br q, *J* 5.5 Hz), −0.33 (1H, br q, *J* 5 Hz); δ_C (125 MHz, $CDCl_3$): 108.27, 77.88, 70, 37.4, 33.3, 31.9, 30.2, 30, 29.7 (v. broad), 29.6, 29.36, 28.7, 27.1, 26.88, 25.74, 23.87, 22.68, 20, 19.2, 15.76, 14.1, 10.9, 9.04; ν_{max}: 2923, 2852, 1062 cm^{-1}.

2.1.21. *cis*-(1*R*,2*R*)-2-[(*S*)-1-Methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]cyclopropanecarbaldehyde (26). Periodic acid (0.6 g, 2.3 mmol) was added to a stirred solution of (*S*)-2,2-dimethyl-4-{(1*R*,2*R*)-2-[(*S*)-1-methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]-cyclopropyl} [1,3]dioxolane (0.7 g, 1.11 mmol) in dry ether (30 ml) under nitrogen at room temperature. The mixture was stirred for 16 h, when TLC showed no starting material. The precipitate was removed and the solvent was evaporated to give a residue; chromatography (10:1 petroleum/ether) gave *cis-(1R,2R)-2-[(S)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyl) tridecyl]cyclopropanecarbaldehyde* (**26**) as a white solid

(0.6 g, 97%), mp 35–37 °C [Found M^+: 558.5751, $C_{39}H_{74}O$ requires: 558.5740], $[\alpha]_D^{24}$ −0.096 (*c* 1.04, $CHCl_3$); which showed δ_H (500 MHz, $CDCl_3$): 9.38 (1H, d, *J* 6 Hz), 1.97–1.91 (1H, m), 1.45–1.17 (61H, br m), 1.09 (3H, d, *J* 6.5 Hz), 0.93 (3H, t, *J* 6.5 Hz), 0.91–0.88 (1H, m), 0.72–0.65 (2H, m), 0.61 (1H, dt, *J* 3.5, 8 Hz), −0.29 (1H, br q, *J* 4.5 Hz); δ_C (125 MHz, $CDCl_3$): 201.76 (−), 37.41 (+), 32.3 (−), 32.03 (−), 31.9 (+), 30.2 (+), 29.86 (+), 29.73 (+), 29.7(+) (v. broad), 29.65 (+), 29.6 (+), 29.36 (+), 28.7 (+), 28.66 (−), 26.8 (+), 22.68 (+), 20.1 (−), 15.77 (−), 14.1 (−), 13.6 (+), 10.9 (+); ν_{max}: 2917, 2852, 1692 cm^{-1}.

2.1.22. *trans*-(1*S*,2*R*)-2-[(*S*)-1-Methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]cyclopropanecarbaldehyde (27). Sodium methoxide (0.053 g, 0.985 mmol) was added to a stirred solution of *cis*-(1*R*,2*R*)-2-[(*S*)-1-methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]cyclopropanecarbaldehyde (0.5 g, 0.896 mmol) in methanol (15 ml) and tetrahydrofuran (10 ml) and refluxed for 56 h. The mixture was cooled to room temperature, quenched with satd aq ammonium chloride (20 ml), and extracted with 1:1 petroleum/ether (3×30 ml). The combined organic layers were dried and evaporated to yield a thick oil which solidified later as a mixture of trans- and cis-isomers in the ratio 22:1. Chromatography (10:0.5 petroleum/ether) gave *trans-(1S,2R)-2-[(S)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyl) tridecyl]cyclopropanecarbaldehyde* (**27**) as a jelly-like solid (0.35 g, 70%) [Found M^+: 558.5756, $C_{39}H_{74}O$ requires: 558.5740], $[\alpha]_D^{22}$ +9.6 (*c* 1.15, $CHCl_3$); which showed δ_H (500 MHz, $CDCl_3$): 9.00 (1H, d, *J* 5.65 Hz), 1.72–1.68 (1H, m), 1.44–1.22 (59H, br m), 1.19–1.13 (2H, br m), 0.99 (3H, br s), 0.98–0.92 (1H, m), 0.91 (3H, t, *J* 7 Hz), 0.69–0.64 (2H, br m), 0.58 (1H, dt, *J* 4.1, 8.2 Hz), −0.31 (1H, br q, *J* 5 Hz); δ_C (125 MHz, $CDCl_3$): 201, 36.8, 31.93, 30.42, 30.22, 29.88, 29.73, 29.7 (v. broad), 29.62, 29.36, 29.27, 28.72, 27.03, 22.7, 19.35, 15.77, 14.11, 13.27, 10.9; ν_{max}: 2921, 2848, 1690 cm^{-1}.

2.1.23. 5-(7-Bromo-heptylsulfanyl)-1-phenyl-1*H*-tetrazole. Diethyl azodicarboxylate (5.36 g, 30.76 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred solution of 7-bromoheptan-1-ol (5 g, 25.6 mmol), triphenylphosphine (8.74 g, 33.3 mmol) and 1-phenyl-1H-tetrazol-5-thiol (5.48 g, 30.76 mmol) in tetrahydrofuran (100 ml) at 5 °C under nitrogen. The mixture was allowed to reach room temperature and stirred for 24 h, then the solvent was evaporated and the residue was dissolved in ether (150 ml) and petroleum (50 ml) and stirred for 15 min. The precipitate was removed through a pad of Celite and the filtrate was evaporated to give a pale yellow oil. This was dissolved in ether and suspended on silica and then columned (1:1 petroleum/ether) to give 5-(7-bromoheptylsulfanyl)-1-phenyl-1*H*-tetrazole as a pale yellow oil (5 g, 55%) [Found M^+: 356.0509; $C_{14}H_{19}N_4Br^{81}$ requires: 356.0493], which showed δ_H (250 MHz, $CDCl_3$): 7.55 (5H, br s), 3.38 (4H, br t, *J* 6.4 Hz), 1.82 (4H, br s), 1.47 (6H, br s); δ_C (62.5 MHz, $CDCl_3$): 154.4, 133.66, 130.1, 129.76, 123.8, 33.89, 33.21, 32.57, 28.94, 28.37, 28.1, 27.9; ν_{max}: 2931, 2855, 1499, 1411, 761, 694 cm^{-1}.

2.1.24. 1-Phenyl-5-[17-(tetrahydropyran-2-yloxy)heptadecylsulfanyl]-1*H*-tetrazole. 1-Bromo-10-tetrahydropyranyloxydecane (5.7 g, 17.7 mmol) in dry tetrahydrofuran (15 ml) was added dropwise to a suspension of magnesium turnings (0.56 g, 23 mmol) in dry tetrahydrofuran (20 ml) under nitrogen. Once the exothermic reaction had subsided, the mixture was refluxed for 1 h then cooled to room temperature. The Grignard reagent was added to a stirred solution of 5-(7-bromoheptylsulfanyl)-1-phenyl-1*H*-tetrazole (4.5 g, 12.67 mmol) in tetrahydrofuran (30 ml) at 5 °C. The mixture was cooled to −40 °C followed by the addition of dilithium tetrachlorocuprate (2.5 ml), stirred for 2 h at this temperature and at room temperature for 12 h, then satd aq ammonium chloride (100 ml) was added together with ether (100 ml). The organic layer was separated and the aqueous layer was re-extracted with ether (2×50 ml). The combined organic layers were washed with water, dried and evaporated to give a residue; chromatography (5:2 petroleum/ether) gave *1-phenyl-5-[17-(tetrahydropyran-2-yloxy)heptadecylsulfanyl]-1H-tetrazole* as a colourless oil (2 g, 31%), which showed δ_H (250 MHz, $CDCl_3$): 7.57 (5H, br s), 4.57 (1H, br t, *J* 3.9 Hz), 3.82–3.89 (1H, m), 3.74 (1H, dt, *J* 7, 9.4 Hz), 3.52–3.46 (1H, m), 3.42–3.32 (4H, including a triplet with coupling constant 7.5 Hz), 1.85–1.75 (4H, m), 1.58–1.22 (31H, br m); δ_C (62.5 MHz, $CDCl_3$): 154.5, 133.7, 130, 129.7, 123.8, 98.8, 67.67, 62.3, 33.8, 33.34, 33.2, 32.6, 30.76, 29.6 (v. broad), 29, 28.6, 28.4, 28.1, 27.9, 26.2, 25.5, 19.7; ν_{max}: 2916, 2852, 1499, 1033, 760 cm^{-1}.

2.1.25. 1-Phenyl-5-[17-(tetrahydro-pyran-2-yloxy)heptadecane-1-sulfonyl]-1*H*-tetrazole (30). To a stirred solution of 1-phenyl-5-[17-(tetrahydropyran-2-yloxy)heptadecylsulfanyl]-1*H*-tetrazole (1.5 g, 2.9 mmol) in methylated spirit (30 ml) was added dropwise a yellow solution of ammonium heptamolybdate(VI) tetra-hydrate (0.34 g, 0.27 mmol), in 35% H_2O_2 (w/w) (1.4 ml, 14.5 mmol) at 10 °C. The resulting yellow solution was stirred for 1 h at this temperature and then for 16 h at room temperature. The solvent was then evaporated to give a yellow solid, which was treated with water (50 ml) and satd aq sodium bicarbonate (25 ml) and then the product was extracted with dichloromethane (3×50 ml). The combined organic layers were washed with brine (50 ml), dried and evaporated to give the crude product. Chromatography (5:3 petroleum/ethyl acetate) gave a white solid, *17-(1-phenyl-1H-tetrazole-5-sulfonyl)-heptadecan-1-ol* (0.8 g, 59%), mp 65–67 °C [Found M^+: 464.2817; $C_{24}H_{40}O_3SN_4$ requires: 464.2821], which showed δ_H (250 MHz, $CDCl_3$): 7.71–7.55 (5H, m), 3.73 (2H, br t, *J* 7.9 Hz), 3.63 (2H, t, *J* 6.4 Hz), 1.97–1.88 (2H, br m), 1.81–1.25 (29H, br m); δ_C (62.5 MHz, $CDCl_3$): 153.45, 133, 131.4, 129.7, 125.1, 63.1, 55.97, 32.7, 29.6, 29.4, 29.1, 28.8, 28.1, 25.7, 21.9; ν_{max}: 3430, 1496, 1464, 1339, 1149, 909 cm^{-1}. Pyridinium *p*-toluenesulfonate (65 mg, 0.258 mmol) was added to a stirred solution of the alcohol (0.8 g, 1.7 mmol) and 3,4-dihydro-2*H*-pyran (0.3 g, 3.45 mmol) in dry dichloromethane (30 ml) under nitrogen at room temperature. The mixture was stirred for 2 h, when TLC showed no starting material, quenched with satd aq sodium bicarbonate (15 ml), water (10 ml) and extracted with dichloromethane (3×20 ml). The combined organic layer was dried and evaporated; chromatography of the residue, eluting with petroleum/ethyl acetate (5:1.5) gave a white solid, *1-phenyl-5-[17-(tetrahydropyran-2-yloxy) heptadecane-1-sulfonyl]-1H-tetrazole* (**30**) (0.93 g, 98%), mp 56–58 °C [Found $M-H^+$: 547.3327; $C_{29}H_{48}O_4SN_4$ requires:

547.3318], which showed δ_H (250 MHz, $CDCl_3$): 7.71–7.60 (5H, m), 4.58 (1H, t, *J* 3.9 Hz), 3.95–3.83 (1H, m), 3.77–3.71 (3H, m), 3.58–3.50 (1H, m), 3.43–3.34 (1H, m), 2.05–1.89 (2H, m), 1.85–1.22 (34H, br m); δ_C (62.5 MHz, $CDCl_3$): 153.5, 133.7, 131.4, 129.7, 125.1, 98.8, 67.7, 62.3, 56.00, 30.7, 29.64, 29.2, 28.9, 28.13, 26.2, 25.5, 21.9, 19.7; ν_{max}: 2924, 2852, 1497, 1465, 1342, 1152 cm^{-1}.

2.1.26. 18-{(1*S*,2*R*)-2-[(*S*)-1-Methyl-13-((1*R*,2*S*)-2-octadec-ylcyclopropyl)tridecyl]cyclopropyl}octadecan-1-ol. Lithium hexamethyldisilazide (0.81 ml, 0.81 mmol) was added dropwise to a stirred solution of tetrazole **30** (0.294 g, 0.537 mmol) and *trans*-(1*S*,2*R*)-2-[(*S*)-1-methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]cyclopropanecarbaldehyde (0.25 g, 0.45 mmol) in dry tetrahydrofuran (15 ml) under nitrogen at 2–4 °C. The reaction was exothermic and the temperature rose to 6 °C, resulting in a yellow solution. This was allowed to reach room temperature and stirred for 2 h, when TLC showed no starting material. It was cooled to 0 °C and quenched with satd aq ammonium chloride (3 ml). The product was extracted with 1:1 petroleum/ether (3×30 ml); the combined organic layers were washed with brine, dried and evaporated to give a thick yellow oil; chromatography (10:0.5 petroleum/ether) gave *(E/Z)-2-(18-{(1R,2R)-2-[(S)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyl)tridecyl]cyclopropyl}octadec-17-enyloxy) tetrahydropyran* (**31**) (0.36 g, 90%). *p*-Toluenesulfonic acid monohydrate (0.14 g, 0.738 mmol) was added to a stirred solution of (*E*/*Z*)-mixture **31** (0.325 g, 0.37 mmol) in tetrahydrofuran (15 ml) and methanol (4 ml) at room temperature. The mixture was stirred for 3 h, when TLC showed no starting material, then quenched with satd aq sodium bicarbonate (15 ml) and extracted with petroleum/ether (1:1) (3×30 ml). The combined organic layers were washed with brine (15 ml), water (15 ml), dried and evaporated, to give a white solid, *(E/Z)-18-{(1R,2R)-2-[(R)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyl)tridecyl]cyclopropyl}octadec-17-en-1-ol* (0.28 g, 95%) which was used for the next step without purification. Sodium metaperiodate (1.34 g, 6.3 mmol) in hot water (25 ml) was added over 45 min to a stirred solution of the above (*E*/*Z*) mixture (0.25 g, 0.314 mmol) in isopropyl alcohol (30 ml), acetic acid (1 ml), satd aq copper sulfate (1 ml) and hydrazine hydrate (5 ml) at 60 °C. The temperature rose to 80 °C through the addition. The mixture was stirred for 2 h to reach room temperature then extracted with petroleum/ether (1:1) (2×50 ml), dried and evaporated to give a white solid. The reduction was repeated in order to complete the hydrogenation. Chromatography of the crude product (5:1 petroleum/ether) gave *18-{(1S,2R)-2-[(S)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyl)tridecyl]cyclopropyl}octadecan-1-ol* (0.21 g, 85%), mp 60–62 °C [Found M^+: 798.8540, $C_{56}H_{110}O$ requires: 798.8557], $[\alpha]_D^{22}$ +2.44 (*c* 1.23, $CHCl_3$); which showed δ_H (500 MHz, $CDCl_3$): 3.65 (2H, t, *J* 6.6 Hz), 1.61–1.55 (2H, pent, *J* 6.6 Hz, and 1H, br s, for the hydroxyl group), 1.43–1.22 (86H, br m), 1.20–1.12 (4H, m), 0.904 (3H, d, *J* 6.65 Hz), 0.89 (3H, t, *J* 7 Hz), 0.69–0.63 (3H, m), 0.57 (1H, br dt, *J* 4.1, 8.2 Hz), 0.48–0.42 (1H, m), 0.22–0.18 (1H, m), 0.17–0.14 (1H, m), 0.13–0.09 (1H, m), −0.32 (1H, br q, *J* 4.75 Hz), δ_C (125 MHz, $CDCl_3$): 63.1 (+), 38.1 (−), 37.43 (+), 34.49 (+), 32.84 (+), 31.93 (+), 30.23 (+), 30.08 (+), 29.71 (+, v. broad), 29.66 (+), 29.62 (+), 29.44 (+), 29.36 (+), 28.73 (+), 27.26 (+), 26.15 (−), 25.75 (+), 22.69 (+), 19.69 (−), 18.63 (−), 15.79 (−), 14.1 (−), 10.92 (+), 10.5 (+); ν_{max}: 3406, 2910, 1215, 1056 cm^{-1}.

2.1.27. 18-{(1*S*,2*R*)-2-[(*S*)-1-Methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]cyclopropyl}octadecanal (32). 18-{(1*S*,2*R*)-2-[(*S*)-1-Methyl-13-((1*R*,2*S*)-2-octadecylcyclopropyl)tridecyl]cyclopropyl}octadecan-1ol (0.15 g, 0.188 mmol) was dissolved in hot dichloromethane (5 ml) and added to a refluxing stirred suspension of pyridinium chlorochromate (0.1 g, 0.47 mmol) in dichloromethane (15 ml). The mixture was refluxed and stirred vigorously for 2 h, when TLC showed no starting material. The mixture was cooled to room temperature and poured into diethyl ether (50 ml), then the precipitate was filtered through a bed of silica and washed well with ether and the filtrate was evaporated to give a white solid. Chromatography (5:1 petroleum/ether) gave *18-{(1S,2R)-2-[(S)-1-methyl-13-((1R,2S)-2-octadecylcyclopropyltridecyl]cyclopropyl}octadecanal* as a white solid (**32**) (0.12 g, 80.5%), mp 48–50 °C [Found M^+: 796.8361, $C_{56}H_{108}O$ requires: 796.8400], $[\alpha]_D^{22}$ +2.8 (*c* 1.02, $CHCl_3$) which showed δ_H (500 MHz, $CDCl_3$): 9.77 (1H, t, *J* 1.8 Hz, C*H*O), 2.42 (2H, dt, *J* 1.6, 7.25 Hz, CH_2CHO),1.63 (2H, pent, *J* 7.22 Hz, CH_2CH_2CHO), 1.42–1.24 (82H, m, satd alkane), 1.23–1.12 (6H, m, satd alkane), 0.90 (3H, d, *J* 6.65 Hz, α-Me), 0.89 (3H, t, *J* 7 Hz, terminal CH_3), 0.71–0.62 (3H, m, 2×C*H*-*cis*-cyclopropane and C*H*CH_3), 0.57 (1H, dt, *J* 4.3, 8.0 Hz, CH_2-*cis*-cyclopropane), 0.48–0.42 (1H, m, CH-*trans*-cyclopropane), 0.22–0.178 (1H, m, CH-*trans*-cyclopropane), 0.169–0.138 (1H, m, CH_2-*trans*-cyclopropane), 0.128–0.093 (1H, m, CH_2-*trans*-cyclopropane), −0.32 (1H, dt, *J* 4.3, 5.3 Hz, CH_2-*cis*-cyclopropane); δ_C (125 MHz, $CDCl_3$): 202.84 (−), 43.92 (+), 38.11 (−), 37.43 (+), 34.49 (+), 31.93 (+), 30.23 (+), 30.08 (+), 29.7 (+, v. broad), 29.66 (+), 29.61 (+), 29.59 (+), 29.44 (+), 29.36 (+), 29.18 (+), 28.73 (+), 27.27 (+), 26. 15 (−), 22.68 (+), 22.11 (+), 19.67 (−), 18.62 (−), 15.79 (−), 14.1 (−), 10.92 (+), 10.49 (+); ν_{max}: 2918, 2847, 1720 cm^{-1}.

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References and notes

1. (a) Minnikin, D. E. *The Biology of the Mycobacteria*; Ratledge, C., Stansford, J., Eds.; Academic: London, 1982; p 95; (b) Brennan, P. J.; Nikaido, H. *Annu. Rev. Biochem.* **1995**, *64*, 29–63; (c) Asselineau, J.; Laneelle, G. *Front. Biosci.* **1998**, *3*, 164–174; (d) Minnikin, D. E.; Kremer, L.; Dover, L. G.; Besra, G. S. *Chem. Biol.* **2002**, *9*, 545–553; (e) Barry, C. E.; Lee, R. E.; Mdluli, K.; Sampson, A. E.; Schroeder, B. G.; Slayden, R. A.; Yuan, Y. *Prog. Lipid Res.* **1998**, *37*, 143–179.
2. (a) Minnikin, D. E.; Polgar, N. *J. Chem. Soc., Chem. Commun.* **1967**, 916–918; (b) Minnikin, D. E.; Polgar, N. *J. Chem. Soc., Chem. Commun.* **1967**, 1172–1177.
3. George, K. M.; Yuan, Y.; Sherman, D. S.; Barry, C. E. *J. Biol. Chem.* **1995**, *272*, 27292–27298.
4. (a) Dobson G.; Minnikin D. E.; Minnikin S. M.; Parlett J. H.; Goodfellow M. *Chemical Methods in Bacterial Systematics*; Minnikin, D. E., Goodfellow, M., Eds.; Academic: London;

237 pp; (b) Minnikin, D. E.; Polgar, N. *J. Chem. Soc., Chem. Commun.* **1967**, 1172–1174; (c) Minnikin, D. E.; Minnikin, S. M.; Goodfellow, M.; Stanford, J. L. *J. Gen. Microbiol.* **1982**, *128*, 817–822.
5. Yuan, Y.; Crane, D. C.; Musser, J. M.; Sreevatsan, S.; Barry, C. E. *J. Biol. Chem.* **1997**, *272*, 10041–10049.
6. Lacave, C.; Lanéelle, M.-A.; Daffé, M.; Montrozier, H.; Rols, M.-P.; Asselineau, C. *Eur. J. Biochem.* **1987**, *163*, 369–378.
7. (a) Daffé, M.; Lanéelle, M.-A.; Lacave, C. *Res. Microbiol.* **1991**, *142*, 397–403; (b) Dubnau, E.; Lanéelle, M.-A.; Soares, S.; Benichou, A.; Vaz, T.; Prome, D.; Daffé, M.; Quemard, A. *Mol. Microbiol.* **1997**, *23*, 313–322; (c) Laval, F.; Laneelle, M.-A.; Deon, C.; Monsarrat, B.; Daffe, M. *Anal. Chem.* **2001**, *73*, 4537–4544.
8. Watanabe, M.; Aoyagi, Y.; Mitome, H.; Fujita, T.; Naoki, H.; Ridell, M.; Minnikin, D. E. *Microbiology* **2002**, *148*, 1881–1902.
9. Watanabe, M.; Aoyagi, Y.; Ridell, M.; Minnikin, D. E. *Microbiology* **2001**, *147*, 1825–1837.
10. Watanabe, M.; Ohta, A.; Sasaki, S.-I.; Minnikin, D. E. *J. Bacteriol.* **1999**, *181*, 2293–2297; Fujita, Y.; Naka, T.; Doi, T.; Yano, I. *Microbiology* **2005**, *151*, 1443–1452; Wax esters have also been shown to be present in trehalose monomycolates from *M. avium-intracellulare*, *M. phlei* and *M. flavescens*, though it is not clear whether these contain α-methyl-*trans*-cyclopropanes.
11. See e.g., (a) He, H.; Oka, S.; Yamamura, Y.; Kusunose, E.; Kusunose, M.; Yano, I. *Microbiol. Immunol.* **1991**, *76*, 201–204; (b) Maekura, R.; Nakagawa, M.; Nakamura, Y.; Hiraga, T.; Yamamura, Y.; Ito, M.; Ueda, E.; Yano, S.; He, H.; Oka, S.; Kashima, K.; Yano, I. *Am. Rev. Respir. Dis.* **1993**, *148*, 997–1001; (c) Pan, J.; Fujiwara, N.; Oka, R.; Ogura, T.; Yano, I. *Microbiol. Immunol.* **1999**, *43*, 863–869; (d) Liu, J.; Barry, C. E.; Besra, G. S.; Nikaido, H. *J. Biol. Chem.* **1996**, *271*, 29545–29551.
12. (a) Asselineau, C.; Asselineau, J. *Bull. Soc. Chim. Fr.* **1966**, 1992–1999; (b) Tocanne, J. F.; Asselineau, C. *Bull. Soc. Chim. Fr.* **1968**, 4519–4525; (c) Asselineau, C.; Tocanne, G.; Tocanne, J. F. *Bull. Soc. Chim. Fr.* **1970**, 1455–1459.
13. Lacave, C.; Lanéelle, M.-A.; Daffé, M.; Montrozier, H.; Rols, M.-P.; Asselineau, C. *Eur. J. Biochem.* **1987**, *163*, 369–378.
14. (a) Al-Dulayymi, J. R.; Baird, M. S.; Roberts, E. *J. Chem. Soc., Chem. Commun.* **2003**, 228–229; (b) Al-Dulayymi, J. R.; Baird, M. S.; Roberts, E. *Tetrahedron* **2005**, *61*, 11939–11951; (c) Al-Dulayymi, J. R.; Baird, M. S.; Roberts, E. *Tetrahedron Lett.* **2000**, *41*, 7107–7110.
15. Astola, J.; Munoz, M.; Sempere, M.; Coll, P.; Luquin, M.; Valero-Guillen, P. L. *Microbiology* **2002**, *148*, 3119–3127.
16. See e.g., (a) Lee, R. E.; Armour, J. W.; Takayama, K.; Brennan, P. J.; Besra, G. S. *Biochim. Biophys. Acta* **1997**, *1346*, 275–284; (b) Grogan, D. W.; Cronan, J. E. *Microbiol. Mol. Biol. Rev.* **1997**, *61*, 429–441; (c) Asselineau, C.; Asselineau, J.; Lanéelle, G.; Lanéelle, M.-A. *Prog. Lipid Res.* **2002**, *41*, 501–523; (d) Kremer, L.; Baulard, A. R.; Besra, G. S. *Molecular Genetics of Mycobacteria*; Hatfull, G. F., Jacobs, W. R., Eds.; American Soc. Microbiology: Washington, DC, 2000; p 173; (e) Yuan, Y.; Mead, D.; Schroeder, B. G.; Yu, Y. Q.; Barry, C. E. *J. Biol. Chem.* **1998**, *273*, 21282–21290; (f) Yuan, Y.; Crane, D. C.; Musser, J. M.; Sreevatsan, S.; Barry, C. E. *J. Biol. Chem.* **1997**, *272*, 10041–10049.
17. Yuan, Y.; Barry, C. E. *Proc. Natl. Acad. Sci.* **1996**, *93*, 12828–12833.
18. Schroeder, B. G.; Barry, C. E. *Bioorg. Chem.* **2001**, *29*, 164–177.
19. Glickman, M. S.; Cahill, S. M.; Jacobs, W. R. *J. Biol. Chem.* **2001**, *276*, 2228–2233.
20. Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97–103; Martin, B. K. D.; Mann, J.; Sageot, O. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2455–2460.
21. Coxon, G. D.; Al-Dulayymi, J. R.; Baird, M. S.; Knobl, S.; Roberts, E.; Minnikin, D. E. *Tetrahedron: Asymmetry* **2003**, 1211–1222; See also, e.g., reference 25.
22. Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1991**, *47*, 1215–1230.
23. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175–1178; Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, 336–357; Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, 856–878; (b) See e.g., Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28; Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1999**, 1209–1215; Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 356–366.
24. Jorgenson, M. J. *J. Am. Chem. Soc.* **1969**, *91*, 6432–6443.
25. Barloy-Da Silva, C.; Benkonider, A.; Pale, P. *Tetrahedron Lett.* **2000**, *41*, 3077–3081.
26. Mitome, H.; Miyaoka, H.; Nakano, M.; Yamada, Y. *Tetrahedron Lett.* **1995**, *36*, 8231–8234.
27. Honda, T.; Katoh, M.; Yamane, S.-I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2291.
28. Fujimoto, Y.; Ohhana, M.; Terasawa, T.; Ikekawa, N. *Tetrahedron Lett.* **1985**, *26*, 3239–3242; See also, Cossy, J.; Blanchard, N.; Defoosseux, M.; Meyer, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2144–2146.