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# Synthesis of methyl 3-(2-octadecylcyclopropen-1-yl)propanoate and methyl 3-(2-octadecylcyclopropen-1-yl)pentanoate and cyclopropane fatty acids as possible inhibitors of mycolic acid biosynthesis

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**Abstract**

(*Z*)-Tetracos-5-enoic acid is a key intermediate in the biosynthesis of mycobacterial mycolic acids. Recently the methyl ester of its cyclopropene analogue, methyl 4-(2-octadecylcyclopropen-1-yl)butanoate, was shown to act as an inhibitor of mycolic acid biosynthesis. The related analogues methyl 5-(2-octadecylcyclopropen-1-yl)pentanoate and methyl 3-(2-octadecylcyclopropen-1-yl)propanoate have been synthesised, as well as the related cyclopropane esters methyl (*Z*)-4-(2-octadecylcyclopropan-1-yl)butanoate and methyl (*Z*)-5-(2-octadecylcyclopropan-1-yl)pentanoate. The synthesis of methyl 3-(2-octadecylcyclopropen-1-yl)propanoate involved protection of the cyclopropene ring by iodination to allow oxidation of an alcohol to a carboxylic acid; the diiodocyclopropane was deprotected by a new mild procedure using activated zinc.

*Key words:* Mycolic acid; Biosynthetic intermediate; Inhibitor; Tetracosenoic acid; Cyclopropene fatty acid; Cyclopropane fatty acid; Diiodocyclopropane; Activated zinc

## 1. Introduction

Rising numbers of tuberculosis infections among certain population groups have increased the need for a better understanding of biosynthetic pathways and their possible inhibition in myco-

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*Abbreviations:* DMSO, dimethylsulfoxide; EI, electron-impact; HMPA, hexamethylphosphordiamide; IR, infra-red; NMR, nuclear magnetic resonance; TBAH, tetrabutylammonium hydroxide; THF, tetrahydrofuran; THP, tetrahydropyran; TLC, thin-layer chromatography.


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bacteria. One characteristic of these bacteria is their extremely lipid-rich cell envelope, whose outer membrane consists largely of mycolic acids, covalently bound to an arabinogalactan [1]. These mycolic acids are 2-alkyl-3-hydroxy fatty acids which may contain further oxygen functionalities [1].

The biosynthesis of mycolic acids has been studied by Takayama and co-workers [2], and (*Z*)-tetracos-5-enoic acid (**1**), formed by a Δ5-desaturase, has been suggested as one of the key initial intermediates. Recently, (*Z*)-tetracos-5-enoic acid has been synthesized [3] and was shown to stimulate mycolic acid biosynthesis in a cell-free extract of *Mycobacterium smegmatis*. [4] Desaturases are known to be inhibited by cyclopropene fatty acids [5], so the cyclopropene analogue of methyl (*Z*)-tetracos-5-enoate (**10**) has been synthesized [6] and found to be an inhibitor of mycolic acid biosynthesis [7]. In order to study the substrate specificity of the desaturase, we synthesized cyclopropene fatty acids with a varying number of methylene groups between the ester functionality and the cyclopropene ring and some cyclopropane analogues.

## 2. Experimental procedures

Proton ($^1$H) and carbon ($^{13}$C) nuclear magnetic resonance spectra (NMR) (δ chemical shift values, ppm) were obtained using deuteriochloroform solutions on a Brucker WP 200 instrument; $^1$H signals are labelled 's' (singlet), 'd' (doublet), 't' (triplet), 'q' (quadruplet) and 'm' (multiplet). Electron-impact (EI) mass spectra were recorded on a Kratos MS 80RF spectrometer. Infra-red (IR) spectra were obtained with a Nicolet 20PC Fourier Transform spectrometer; peaks are labelled 'br' (broad), 's' (sharp), 'm' (medium) and 'w' (weak). Melting points (uncorrected) were obtained on a Kofler hot-stage apparatus. Elementary analyses were performed on a Carlo-Erba Instrumentazione 1106 CHN analyser. Starting materials were purchased from Aldrich, Fluka or Lancaster Syntheses. Petrol refers to petroleum ether (b.p. 60–80°C). Fluka 6078 silica gel was used for flash column chromatography. A column of 5 × 18 cm was used for separations on 200-g silica gel, a 3 × 25-cm column for separations on 100–120-g silica gel and a 2 × 25-cm column for separations on 45-g silica gel. Thin-layer chromatography (TLC) was carried out on Merck 5554 silica gel aluminium backed sheets.

### 2.1. 1-Bromo-3-tetrahydropyranyloxypropane (14)

3,4-Dihydro-2H-pyran (6.6 ml, 71.8 mmol) and *para*-toluenesulphonic acid (10 mg) were added to a solution of 3-bromopropan-1-ol (5 g, 35.9 mmol) in dichloromethane (20 ml). The reaction was stirred under nitrogen overnight. The reaction mixture was washed with aqueous saturated sodium bicarbonate and dried ($MgSO_4$), and the solvent was removed in vacuo. Flash column chromatography (petrol:ethyl acetate 95:5, 200 g silica gel) of the residue yielded 1-bromo-3-tetrahydropyranyloxypropane (**14**) as a colourless oil (7.25 g 93%). IR (film) 2942 s, 2872 s, 1441 m, 1352 m, 1202 m, 1134 s, 1119 s, 1076 s, 1034 s, 986 m; $^1$H-NMR (200 MHz) 1.27–1.88 (6H, m, C*H*$_2$ of C-3, C-4, C-5 of the tetrahydropyran (THP) ring), 1.96–2.17 (2H, m, BrCH$_2$C*H*$_2$), 3.44–3.62 (4H, m, BrC*H*$_2$, C*H*$_2$O), 3.79–3.90 (2H, m, C-6 THP), 4.58 (1H, broad t, OC*H*O); $^{13}$C-NMR (50.3 MHz) 19.48 (C4 THP), 25.40 (C5 THP), 30.58 (C2), 30.66 (C3 THP), 32.89 (C1), 62.22 (C6 THP), 64.84 (C3), 98.85 (C2 THP); *m/z* (EI) 222.064 ($M^+$ 1.8%), 121 ($M^+$-OTHP), $C_8H_{15}O_2Br$ requires 222.0255, found C, 43.20; H, 6.68, $C_8H_{15}O_2Br$ requires C, 43.24; H, 6.81%.

### 2.2. 1-Iodo-3-tetrahydropyranyloxypropane (15)

1-Bromo-3-tetrahydropyranyloxypropane (**14**) (7.25 g, 32.5 mmol) was added to a solution of sodium iodide (9.75 g, 65.0 mmol) in dry acetone (100 ml). Sodium bicarbonate (6.6 g, 78.6 mmol) was added and the reaction mixture was heated to reflux overnight. The solvent was removed under reduced pressure, water (50 ml) was added, and the aqueous phase was extracted with diethyl ether (3 × 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The remaining residue was purified by flash column chromatography (petrol:ethyl acetate 95:5, 200 g silica gel) and yielded 1-iodo-3-tetrahydropyranyloxypropane (**15**) as a colourless oil (7.43 g, 85%).

IR (film) 2942 s, 2870 s, 1441 m, 1352 m, 1184 m, 1132 s, 1118 m, 1076 m, 1030 s, 982 w; $^1$H-NMR (200 MHz) 1.44–1.87 (6H, m, C*H*$_2$ of C-3, C-4, C-5 of THP), 1.97–2.09 (2H, m, ICH $_2$C*H*$_2$), 3.24 (2H, t, *J* 7.0 Hz, IC*H*$_2$), 3.33–3.51 (2H, m, C*H*$_2$O), 3.69–3.86 (2H, m, C-6 THP), 4.53 (1H, broad t, OC*H*O), $^{13}$C-NMR (50.3 MHz) 3.53 (C1), 19.51 (C4 THP), 25.47 (C5 THP), 30.62 (C3 THP), 33.59 (C2), 62.29 (C6 THP), 66.84 (C3), 98.88 (C1 THP); *m/z* (EI) 270 ($M^+$ 0.7%), 169 ($M^+$-OTHP), found 270.0161 $C_8H_{15}O_2I$ requires 270.0117; found C, 35.79; H, 5.62, $C_8H_{15}O_2I$ requires C, 35.55; H, 5.60%.

### 2.3. *Reaction of 1,1,2-tribromo-2-octadecylcyclopropane (2) with diiodoalkanes and 1-iodo-3-tetrahydropyranyloxypropane (15)*

1,1,2-Tribromo-2-octadecylcyclopropane was prepared as described earlier [6]. *n*-Butyl lithium (7.2 ml, 9.0 mmol, 1.25 M hexane solution) was added dropwise to a stirring solution of 1,1,2-tribromo-2-octadecylcyclopropane (**2**) (2.16 g, 4.05 mmol) in dry diethyl ether (50 ml) under nitrogen at −78°C. The reaction was stirred for 1 h at 0°C and then allowed to reach room temperature, and hexamethylphosphordiamide (HMPA) (1.2 g, 6.7 mmol) was added. The resulting solution was added to a large excess of the diiodoalkane or 1-iodo-3-tetrahydropyranyloxypropane (**15**) (16.6–40.6 mmol) and the reaction was stirred overnight. After quenching with water (100 ml), the aqueous phase was extracted with diethyl ether (3 × 30 ml). The combined organic layers were washed with water (3 × 30 ml), dried ($MgSO_4$), and evaporated in vacuo. Flash column chromatography (petrol, 120 g silica gel) of the residues yielded the products as colourless oils.

#### 2.3.1. *1-Iodo-3-(2-octadecylcyclopropen-1-yl)propane (4)*

1,1,2-Tribromo-2-octadecylcyclopropane (**2**) (2.16 g, 4.05 mmol) was reacted with 1,3-diiodopropane (5.12 g, 17.0 mmol) to give the title compound (**4**) in a yield of 54% (1.0 g). IR (film) 2924 s, 2853 s, 1682 w, 1466 m, 1377 w, 1096, 1011 m; $^1$H-NMR (200 MHz) 0.79 (2H, s, C*H*$_2$, cyclopropene), 0.89 (3H, t, *J* 6.4 Hz, C*H*$_3$(CH$_2$)$_{17}$), 1.26–1.56 (32H, broad, aliphatic C*H*$_2$), 2.05 (2H, m, CH$_2$C*H*$_2$-CH$_2$I), 2.37 (2H, t, *J* 7.1 Hz, CH$_3$ (CH$_2$)$_{16}$C*H*$_2$), 2.49 (2H, t, *J* 6.8 Hz, C*H*$_2$CH$_2$CH$_2$I), 3.19 (2H, t, *J* 6.9 Hz, CH$_2$CH$_2$C*H*$_2$I); $^{13}$C-NMR (50.3 MHz) 6.18 (C1), 7.42 (CH$_2$ cyclopropene), 14.19 (C23), 22.76 (C22), 26.10 (C6), 27.05 (C3), 27.42 (C7), 29.45–29.51 (C8–C20), 30.62 (C2), 32.01 (C21), 107.35 (C4), 111.18 (C5); *m/z* (EI) 459($M^+$-H), found 459.2437, $C_{24}H_{44}I$ requires 459.2488.

#### 2.3.2. *1-Iodo-4-(2-octadecylcyclopropen-1-yl)butane (5)*

1,1,2-Tribromo-2-octadecylcyclopropane (**2**) (2.16 g, 4.05 mmol) was reacted with 1,4-diiodobutane (12.6 g, 40.6 mmol) to give the title compound (**5**) in a yield of 80% (1.53 g). IR (film) 2924 s, 2853 s, 1682 w, 1466 m, 1377 w 1099, 1009 m; $^1$H-NMR (200 MHz) 0.79 (2H, s, C*H*$_2$, cyclopropene), 0.89 (3H, t, *J* 6.4 Hz, C*H*$_3$(CH$_2$)$_{17}$), 1.26–1.79 (36H, broad, aliphatic C*H*$_2$), 2.19 (4H, m, C*H*$_2$(CH$_2$)$_3$I and CH$_3$(CH$_2$)$_{16}$C*H*$_2$), 3.19 (2H, t, *J* 6.9 Hz CH$_2$CH$_2$C*H*$_2$I); $^{13}$C-NMR (50.3 mHz) 6.51 (C1), 7.46 (CH$_2$ cyclopropene), 14.15 (C24), 22.75 (C23), 24.96 (C4), 26.06 (C7), 27.42 (C8), 28.33 (C3), 29.47–29.77 (C9–C21), 31.98 (C22), 33.16 (C2), 108.50 (C5), 110.34 (C6).

#### 2.3.3. *3-(2-Octadecylcyclopropen-1-yl)tetrahydropyranyloxypropane (16)*

1,1,2-Tribromo-2-octadecylcyclopropane (**3**) (1.5 g, 2.8 mmol) was reacted with 1-iodo-3-tetrahydropyranyloxypropane (**15**) (4.5 g, 16.6 mmol) to give the title compound (**16**) in a yield of 55% (0.51 g). IR (film) 2924 s, 2855 s, 1466 m, 1200 m, 1138 m, 1123 m, 1080 m; $^1$H-NMR (200 MHz) 0.76 (2H, s, C*H*$_2$ cyclopropene), 0.85 (3H, t, *J* 6.4 Hz, C*H*$_3$), 1.22 (32H, broad m, aliphatic C*H*$_2$), 1.47–1.76 (6H, m, C*H*$_2$ of C-3, C-4, C-5 THP), 1.78–1.90 (2H, m, C*H*$_2$CH$_2$OTHP), 2.34 (2H, t, *J* 7.1 Hz, CH$_3$(CH$_2$)$_{16}$C*H*$_2$), 2.45 (2H, t, *J* 7.2 Hz, C*H*$_2$CH$_2$CH$_2$OTHP). 3.32–3.52 (2H, m, C*H*$_2$O), 3.69–3.83 (2H, m, C-6 THP), 4.56 (1H, t, *J* 3.4 Hz, OC*H*O); $^{13}$C-NMR (50.3 MHz) 7.45 (CH$_2$ cyclopropene), 14.15 (C22), 19.53 (C4 THP), 22.75 (C22), 22.86 (C2), 25.54 (C3), 26.04 (C6), 27.42 (C7), 29.41 (C5 THP), 29.74 (C8–C20), 30.76 (C3 THP), 31.98 (C21), 62.20 (C6 THP), 66.95 (C1),

98.82 (C1 THP), 108.72 (C4), 109.97 (C5); *m/z* (EI) 434 ($M^+$ 0.7%), 349 ($M^+$-OTHP), found 434.4086 $C_{29}H_{54}O_2$ requires 434.4124.

### *2.4. Preparation of 1-cyano-ω-(2-octadecylcyclopropen-1-yl)alkanes*

The 1-cyano-ω-(2-octadecylcyclopropen-1-yl)alkanes were prepared by reaction of the iodo compounds with sodium cyanide in dimethylsulfoxide (DMSO) as described earlier [6].

#### *2.4.1. 1-Cyano-3-(2-octadecylcyclopropen-1-yl)propane (**6**)*

1-Iodo-3-(2-octadecylcyclopropen-1-yl)propane (**4**) (1.00 g, 2.2 mmol) was reacted with sodium cyanide (0.12 g, 2.4 mmol) to give the title compound (**6**) in 38% (0.30 g) after purification by flash column chromatography (petrol:ethyl acetate 95:5, 100 g silica gel). $^{13}$C-NMR (50.3 MHz) 7.31 ($CH_2$ cyclopropene), 14.14 (C24), 16.68 (C2), 22.71 (C23), 23.49 (C3), 24.80 (C4), 26.01 (C7), 27.31 (C8), 29.42–29.82 (C9–C21), 31.97 (C22), 106.87 (C5), 111.99 (C6). The signal for C1 was not observed.

#### *2.4.2. 1-Cyano-4-(2-octadecylcyclopropen-1-yl)butane (**7**)*

1-Iodo-4-(2-octadecylcyclopropen-1-yl)butane (**5**) (1.53 g, 3.2 mmol) was reacted with sodium cyanide (0.17 g, 3.5 mmol) to give the title compound (**7**) in a yield of 40% (0.47 g) after purification by flash column chromatography (petrol:ethyl acetate 95:5, 100 g silica gel).

M.p. 37–39°C; IR(film) 2921 s, 2853 s, 2247 m, 1468 m, 1379 w, 1094 m, 1011 m; $^1$H-NMR (200 MHz) 0.72 (2H, s, C*H*$_2$, cyclopropene), 0.81 (3H, t, *J* 6.4 Hz, C*H*$_3$), 1.19–1.66 (36H, broad, aliphatic C*H*$_2$), 2.32 (6H, m, C*H*$_2$ $(CH_2)_2$ C*H*$_2$CN and $CH_3$ $(CH_2)_{16}$C*H*$_2$); $^{13}$C-NMR (50.3 MHz) 7.43 ($CH_2$ cyclopropene), 14.16 (C25), 17.02 (C2), 22.75 (C24), 25.09 (C3 or C5), 26.02 (C8), 26.46 (C3 or C4), 27.38 (C9), 29.41–29.75 (C10–C22), 31.98 (C23), 108.06 (C6), 110.74 (C7), the signal for C1 and one of the carbons C3–C5 were not observed; *m/z* (EI) 73 ($M^+$, 6.0%), found 373.3703, $C_{26}H_{47}N$ requires 373.3709.

### *2.5. Preparation of methyl ω-(2-octadecylcyclopropen-1-yl)alkanoates*

The methyl ω-(2-octadecylcyclopropen-1-yl)-alkanoates were prepared by alkaline hydrolysis and direct phase-transfer catalysed esterification of the intermediate acid as described earlier [6].

#### *2.5.1. Methyl 4-(2-octadecylcyclopropen-1-yl)-butanoate (**10**)*

The title compound (**10**) was prepared from 1-cyano-3-(2-octadecylcyclopropen-1-yl)propane (**6**) (0.14 g, 0.36 mmol) in a yield of 70% (0.12 g), as described earlier [6]. $^{13}$C-NMR (50.3 MHz) 7.43 ($CH_2$ cyclopropene), 14.16 (C24), 22.71 (C23) 22.82 (C3), 25.40 (C4), 26.02 (C7), 27.38 (C8), 29.42–29.73 (C9–C21), 31.97 (C22), 33.56 (C2), 51.45 ($OCH_3$), 108.17 (C5), 110.65 (C6), 173.88 (C1).

#### *2.5.2. Methyl 5-(2-octadecylcyclopropen-1-yl)pentanoate (**11**)*

The title compound (**11**) was prepared from 1-cyano-4-(2-octadecylcyclopropen-1-yl)butane (**7**) (0.48 g, 1.29 mmol) in a yield of 78% (0.39 g) after purification by flash column chromatography (petrol:ethyl acetate 95:5, 100 g silica gel). IR (film) 2924 s, 2855 s, 1743 m, 1466 m, 1363 m, 1169 w, 1094 m, 1011 m; $^1$H-NMR (200 MHz) 0.75 (2H, s, C*H*$_2$, cyclopropene), 0.86 (3H, t, *J* 6.4 Hz, C*H*$_3$), 1.19–1.67 (36H, broad, aliphatic C*H*$_2$), 2.34 (6H, m, C*H*$_2(CH_2)_2$C*H*$_2CO_2CH_3$), and $CH_3$-$(CH_2)_{16}$C*H*$_2$), 3.61 (3H, s, $CO_2$C*H*$_3$); $^{13}$C-NMR (50.3 MHz) 7.39 ($CH_2$ cyclopropene), 14.12 (C25), 22.73 (C24), 24.70 (C3), 25.68 (C5), 26.03 (C8), 26.94 (C4), 27.42 (C9), 29.42–29.74 (C10–C22), 31.98 (C23), 33.88 (C2), 51.42 ($OCH_3$), 108.72 (C6), 110.00 (C7), 174.03 (C1); *m/z* (EI) 406 ($M^+$, 13.8%), 375 ($M^+$-$OCH_3$), 347 ($M^+$-$COOCH_3$), 291 ($M^+$-$(CH_2)_4COOCH_3$), found 406.3811, $C_{27}H_{50}O_2$ requires 406.3811.

### *2.6. Preparation of methyl ω-(2-octadecylcyclopropan-1-yl)alkanoates*

A solution of freshly purified methyl ω-(2-octadecylcyclopropen-1-yl)alkanoate (0.05-0.21

mmol) in diethyl ether (2 ml) was added to a suspension of 10% palladium on charcoal (20–80 mg) in diethyl ether (10 ml) saturated with hydrogen gas. The reaction mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered off over celite and the solution was concentrated in vacuo. The residue was purified by flash chromatography (petrol:diethyl ether 95:5, 45 g silica gel), yielding the methyl (*Z*)-ω-(2-octadecylcyclopropan-1-yl)alkanoate as a colourless oil.

*2.6.1. Methyl(Z)-4-(2-octadecylcyclopropan-1-yl)-butanoate (**12**)*

The title compound (**12**) was prepared from methyl 4-(2-octadecylcyclopropen-1-yl)butanoate (**10**) (84.9 mg, 0.21 mmol) with 80 mg catalyst in a yield of 98% (84.0 mg). IR (film) 2924 s, 2853 s, 1744 s, 1466 m, 1377 w, 1171 m, 1115 w, 738 w; $^1$H-NMR (200 MHz) −0.38 (1H, m, *cis*-H of C3 of the cyclopropane ring), 0.54 (3H, m, *trans*-H of C3 and CH at C1 and C2 of the cyclopropane ring), 0.81 (3H, t, *J* 6.1 Hz, $CH_3$), 1.18 (32H, broad, aliphatic $CH_2$), 1.59–1.63(4H, m, $CH_2$ of C4 and C7), 1.67 (2H, m, $CH_2CH_2CO_2CH_3$), 2.18 –2.33 (2H, t, *J* 7.3 Hz, $CH_2CO_2CH_3$), 3.60 (3H, s, $CO_2CH_3$); *m/z* (EI) 394 ($M^+$, 2.5%), 362 ($M^+$-$CH_3OH$), 334 ($M^+$-$HCOOCH_3$), 320 ($M^+CH_3$-$COOCH_3$), found 394.3874, $C_{26}H_{50}O_2$ requires 394.3811.

*2.6.2. Methyl(Z)-5-(2-octadecylcyclopropan-1-yl)-pentanoate (**13**)*

The title compound (**13**) was prepared from methyl 5-(2-octadecylcyclopropen-1-yl)pentanoate (**11**) (18.8 mg, 0.05 mmol) with 20 mg catalyst in a yield of 90% (17.0 mg). IR (film) 2924 s, 2853 s, 1744 s, 1464 m, 1437 m, 1377 w, 1196 w, 1169 m, 1022 w, 721 w; $^1$H-NMR (200 MHz) −0.35 (1H, m, *cis*-H of C3 of the cyclopropane ring), 0.54 (3H, m, *trans*-H of C3 and CH at C1 and C2 of the cyclopropane ring), 0.86 (3H, t, *J* 6.1 Hz, $CH_3$), 1.24 (40H, broad, aliphatic $CH_3(CH_2)_{17}$, $CH_2$ - $CH_2(CH_2)_2CO_2CH_3$), 1.61–1.67 (2H, m, $CH_2$-$(CH_2)_2CO_2CH_3$), 2.18 –2.33 (2H, t, *J* 7.2 Hz, $CH_2CO_2CH_3$), 3.65 (3H, s, $CO_2CH_3$); *m/z*(EI) 410 ($M^+$2H, 11.1%), 376 ($M^+$-$CH_3OH$), 334 ($M^+$-$CH_3(CH_2)_3COOCH_3$), 292 ($M^+$-$CH_3(CH_2)_3COOCH_3$), found 410.4102, $C_{27}H_{52}O_2$ requires 410.4124.

*2.7. 3-(1,2-Diiodo-2-octadecylcyclopropyl)tetrahydropyranyloxypropane (**17**)*

A solution of iodine (136 mg, 1.08 mmol) in dry diethyl ether (10 ml) was added dropwise to a solution of 3-(2-octadecylcyclopropen-1-yl)tetrahydropyranyloxypropane (**16**) (233 mg, 0.54 mmol) in dry diethyl ether (30 ml) at −78°C under nitrogen. The reaction was allowed to warm up to room temperature and stirred for 75 min The reaction was quenched by the addition of aqueous sodium thiosulfate (20 ml), and the organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by flash column chromatography (petrol, 100 g silica gel), yielding two close running spots of the *cis* and *trans*-isomers of 3-(1,2-diiodo-2-octadecylcyclopropyl)-tetrahydropyranyloxypropane (**17**) as a colourless oil (210 mg, 74%). IR (film) 2924 s, 2853 s, 1466 m, 1199 w, 1138 m, 1121 m 1076 m, 1033 m, 989 w; $^1$H-NMR (200 MHz) 0.86 (3H, t, *J* 6.4 Hz, $CH_3$), 1.24 (32H, broad m, aliphatic $CH_2$), 1.52–2.35 (14H, m, $CH_2$ of C-2, C-3, C-4 of the THP ring, $CH_2CH_2CH_2O$, $CH_3(CH_2)_{16}CH_2$, $CH_2$ of the cyclopropane ring), 3.42–3.52 (2H, m, $CH_2O$), 3.74–3.89 (2H, m, C-6 of the THP ring), 4.09–4.59 (1H, m, OC*H*O); $^{13}$C-NMR (50.3 MHz) 14.20, 19.48, 19.62, 22.75, 24.25, 25.55, 26.34, 28.86, 29.18, 29.43, 29.76, 29.88, 30.16, 30.76, 31.32, 31.97, 35.76, 36.05, 37.46, 40.70, 47.70, 50.73, 62.15, 62.30, 66.14, 66.30, 98.50; *m/z* (EI) 477 ($M^+$-I-THP+H, 38.1%), 349 ($M^+$-2I-THP); found 477.2569, $C_{24}H_{46}IO$ requires 477.2593.

*2.8. 3-(1,2-Diiodooctadecylcyclopropyl)propanol (**18**)*

Pyridinium *para*-toluene sulphonate (23 mg, 0.09 mmol) was added to a stirring solution of 3-(1,2-diiodo-2-octadecylcyclopropyl)tetrahydropyranyloxypropane (**17**) (385 mg, 0.56 mmol) in ethanol (10 ml). The solution was stirred at 55°C for 90 min. Water (10 ml) was added, the ethanol

was evaporated in vacuo, and the aqueous layer was extracted with diethyl ether (3 × 20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash column chromatography (petrol:ethyl acetate 95:5, 100 g silica gel) yielding 3-(1,2-diiodooctadecylcyclopropyl)-propanol (**18**) as a colourless oil (270 mg, 79%). IR (film) 3337 br, 2923 s, 2851 s, 1468 w, 1175 m, 1102 m, 1063 m, 908 w, 735 m; $^1$H-NMR (200 MHz) 0.85 (3H, t, *J* 6.4 Hz, $CH_3$), 1.23 (32H, broad m, aliphatic $CH_2$), 1.48–2.28 (8H, m, $CH_3(CH_2)_{16}CH_2$, $CH_2CH_2CH_2OH$, $CH_2$ of the cyclopropane ring), 3.64–3.74 (2H, m, $CH_2OH$); $^{13}$C-NMR (50.3 MHz) 14.22, 22.77, 23.41, 24.29, 26.02, 26.35, 28.87, 29.18, 29.44, 29.77, 29.87, 31.39, 32.01, 33.12, 34.45, 35.72, 36.06, 36.97, 40.65, 47.23, 50.72, 61.97; *m/z* (EI) 477 ($M^+$-I, 36.1 %), 349 ($M^+$-2I-H), found 477.2610, $C_{24}H_{46}IO$ requires 477.2593.

### 2.9. Methyl 3-(1,2-diiodo-2-octadecylcyclopropyl)-propanoate (20)

A solution of potassium permanganate (0.3 g, 1.9 mmol) in water (5 ml) was stirred vigorously at 0°C for 5 min. Tetrabutylammonium bromide (50 mg, 0.16 mmol) and then a solution of 3-(1,2-diiodooctadecylcyclopropyl)propanol (**18**) (40 mg, 66 mmol) in benzene (3 ml) were added. The reaction was stirred at room temperature overnight. The reaction was quenched by the addition of sodium metabisulphite until the reaction mixture became colourless, and was then acidified with dilute aqueous sulphuric acid (10%). The aqueous layer was extracted with diethyl ether (3 × 20 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was taken up in dichloromethane (2 ml), and aqueous tetrabutylammonium hydroxide (TBAH) (5%, 2 ml) and iodomethane (100 ml) were added. The reaction mixture was stirred for 3 h, then the aqueous layer was removed and the organic layer was washed with water (2 ml) and dried ($MgSO_4$). The solvent was removed in vacuo. The residue was purified by flash column chromatography (petrol: diethyl ether 9:1, 45 g silica gel) yielding methyl 3-(1,2-diiodooctadecylcyclopropyl)-propanoate (**20**) as a colourless oil (24 mg, 47%). IR (film) 2924 s, 2853 s, 1744 s, 1466 m, 1437 m, 1372 w, 1250 w, 1196 m, 1171 m, 1047 w, 993 w, 841 w, 721 w; $^1$H-NMR (200 MHz) 0.85 (3H, t, *J* 6.4 Hz, $CH_3$), 1.23 (32H, broad m, aliphatic $CH_2$), 1.36–1.75 (4H, m, $CH_3(CH_2)_{16}CH_2$, $CH_2CH_2COOCH_3$), 1.97–2.27 (2H, m, $CH_2COOCH_3$), 2.46–2.73 (2H, m, $CH_2$ of the cyclopropane ring), 3.67 and 3.62 (3H, s, $OCH_3$); $^{13}$C-NMR (50.3 MHz) 14.19, 21.79, 22.75, 23.12, 28.81, 29.11, 29.41, 29.74, 29.88, 31.34, 31.98, 34.40, 35.90, 36.05, 46.05, 50.61, 51.80, 172.85; *m/z* (EI) 632 ($M^+$, 0.2 %), 505 ($M^+$-I, 19.5%), 377 ($M^+$-2I-H), found 632.1658, $C_{25}H_{46}I_2O_2$ requires 632.1587.

### 2.10. Reaction of methyl 3-(1,2-diiodo-2-octadecylcyclopropyl)propanoate (20) with n-butyl lithium

To a solution of methyl 3-(1,2-diiodo-2-octadecylcyclopropyl)propanoate (**20**) (90.6 mg, 0.143 mmol) in diethyl ether (5 ml), *n*-butyl lithium (0.14 ml, 0.172 mmol, 1.25 M in hexane) was added at −80°C under nitrogen. After 5 min the reaction was quenched with water (1 ml) at −80°C. More water (3 ml) was added after warming to room temperature, and the products were extracted with diethyl ether (3 × 10 ml) and dried ($MgSO_4$), and the residue was purified by flash column chromatography (petrol:diethyl ether 9:1, 45 g silica gel), yielding starting material and 1,1-dibutyl-3-(2-octadecylcyclopropen-1-yl)propanol (**21**) (18 mg, 27%). IR (film) 3411 b, 2955 m, 2926 s, 2855 s, 1466 m, 1379 w, 1190 w, 1129 w, 1013 w, 721 w; $^1$H-NMR (200 MHz) 0.76 (2H, s, $CH_2$ of the cyclopropene ring), 0.79–0.92 (9H, m, all $CH_3$), 1.23 (32H, broad m, aliphatic $CH_2$), 1.39–1.70(14H, m, $CH_2C((CH_2)_3CH_3)_2OH$), 2.32–2.44 (4H, m, $CH_2CH_2C(Bu)_2OH$ and $CH_3(CH_2)_{16}$-$CH_2$); $^{13}$C-NMR (50.3 MHg) 7.52, 14.15, 20.55, 22.74, 23.37, 25.76, 26.06, 27.48, 29.40, 29.49, 29.73, 31.98, 36.68, 38.85, 74.21, 109.23, 109.85; *m/z* (EI) 462 ($M^+$ 6.6%), 405 ($M^+$-$CH_3CH_2C(Bu)_2OH$), found 462.4790, $C_{32}H_{62}O$ requires 462.4801.

### 2.11. Methyl 3-(2-octadecylcyclopropen-1-yl)propanoate (22)

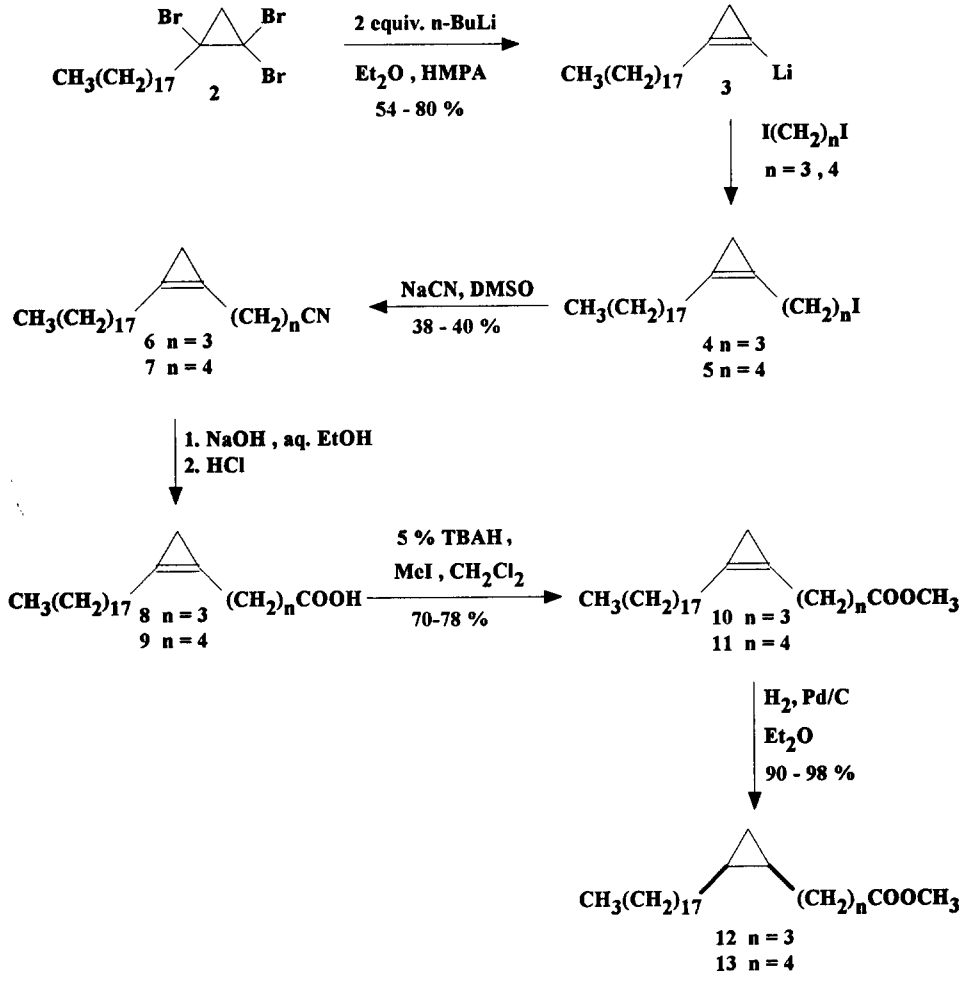
Under an argon atmosphere, lithium (30.0 mg, 4.4 mmol) and naphthalene (0.57 mg, 4.4 mmol) were stirred in dry tetrahydrofuran (THF) (3 ml)

at room temperature for 2 h until all the lithium had dissolved. Zinc chloride (0.30 mg, 2.2 mmol) was dissolved under argon in dry THF (3 ml), and this solution was added dropwise to the lithium solution and stirred for 15 min at room temperature. An aliquot of the above dispersion (103 ml) was transferred to a 1-ml Reacti-vial under argon and cooled to −78°C, and a solution of methyl 3-(1,2-diiodo-2-octadecylcyclopropyl)propanoate (**20**) (24 mg, 38 mmol) in dry THF (0.5 ml) was added. The reaction was left to stir while warming up to room temperature and followed by TLC (petrol). After 3.5 h all starting material had disappeared. The reaction mixture was filtered through filter paper with diethyl ether (10 ml), and the solvent was removed in vacuo. The residue was purified by flash column chromatography (petrol: diethyl ether 9:1, 45 g silica gel), yielding methyl 3-(2-octadecylcyclopropen-1-yl)propanoate (**22**) (12 mg, 84%). IR (film) 2926 s, 2855 s, 1745 s, 1466 m, 1437 m, 1255 m, 1196 m, 1167 m, 1013 w, 735 w; $^1$H-NMR (200 MHz) 0.78 (2H, s, C$H_2$ of the cyclopropene ring), 0.85 (3H, t, $J$ 6.5 Hz, C$H_3$), 1.23 (30H, broad m, aliphatic C$H_2$), 1.50 (2H, m, $CH_3(CH_2)_{15}CH_2$), 2.34 (2H, t, $J$ 6.7 Hz, $CH_2$-$COOCH_3$,), 2.53 (2H, t, $J$ 6.5 Hz, $CH_3(CH_2)_{16}$-$CH_2$), 2.70 (2H, t, $J$ 6.7 Hz, $CH_2CH_2COOCH_3$), 3.66 (3H, s, $OCH_3$); $^{13}$C-NMR (50.3 MHz) 7.54 ($CH_2$ cyclopropene), 14.18 (C23), 21.98 (C3), 22.75 (C22), 25.94 (C6), 27.35 (C7), 29.47–29.73 (C9–C20), 31.98 (C21), 32.20 (C2), 51.68 ($OCH_3$), 107.61 (C4), 111.18 (C5), 173.51 (C1), a small unassigned peak at 34.18; *m/z* (EI) 378 ($M^+$ 33.0%), 363 (M-$CH_3$), 347 (M-$OCH_3$), found 378.3434, $C_{25}H_{46}O_2$ requires 378.3498; found: C, 79.61; H, 12.14, $C_{24}H_{46}O$ requires C, 79.30; H, 12.25%.

## 3. Results and discussion

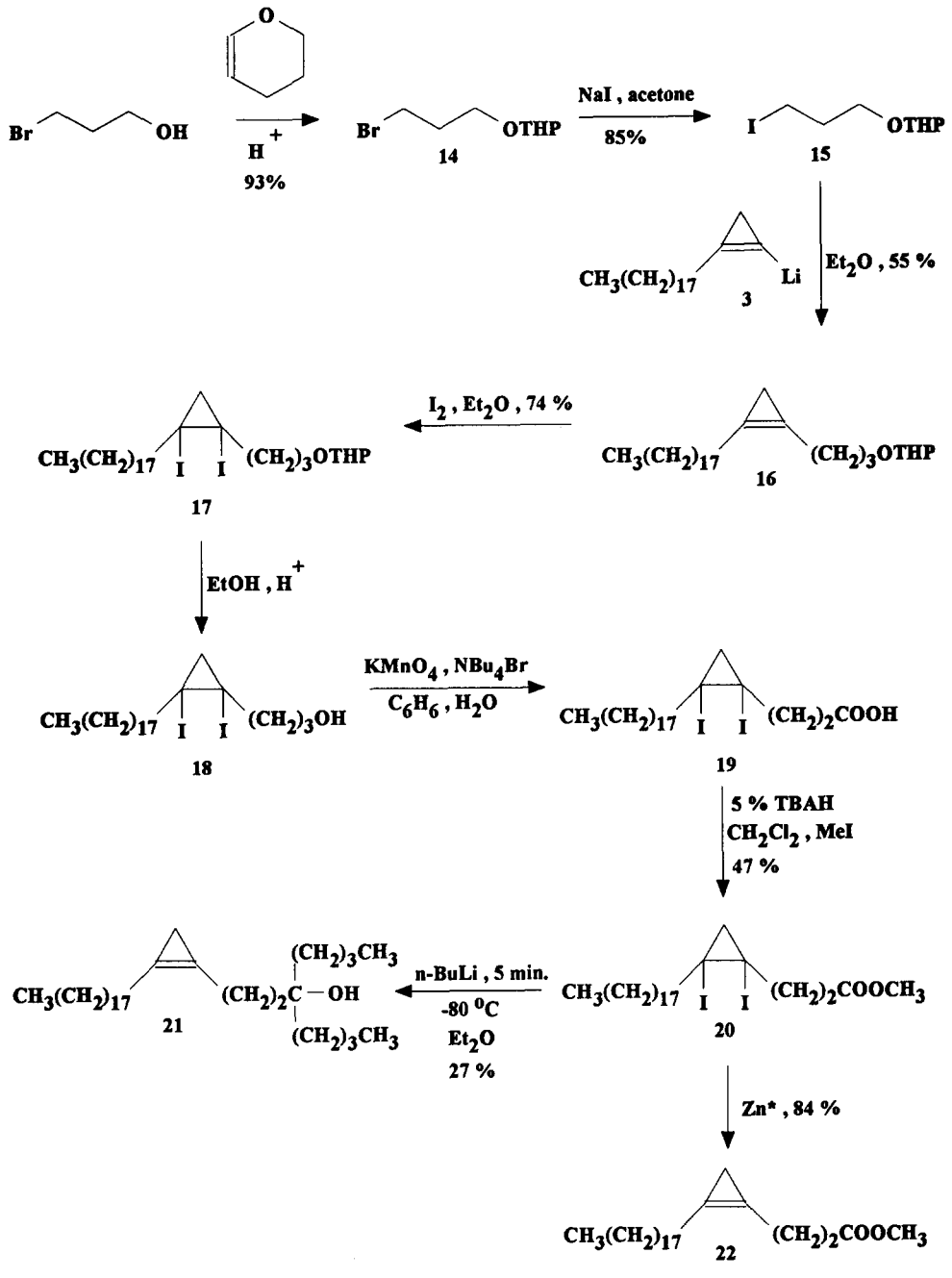
The strategy employed to synthesise methyl 5-(2-octadecyl-cyclopropene-1-yl)-pentanoate (**11**) is outlined in Scheme 1. It is analogous to the strategy employed in the synthesis of methyl 4-(2-octadecylcyclopropen-1-yl)butanoate (**10**). The key step in this synthesis is the coupling reaction between 1,1,2-tribromo-2-octadecyl-cyclopropane (**2**) and a diiodoalkane. The tribromocyclopropane was obtained as previously described [6]. Its reaction with lithium bromide at −78°C leads to a lithium bromide exchange followed by the elimination of lithium bromide. Upon warming to 0°C, a second lithium bromide exchange leads to the formation of 1-lithio-2-octadecylcyclopropene (**3**), which was allowed to react with an iodoalkane. Previous work indicated that the yields decreased with decreasing size of the diiodide employed, and it was disappointingly low (23%) for the coupling with diiodopropane [6]. By-products formed in this reaction seemed to be large hydrocarbons due to the reaction of the remaining iodide atom in the product with another equivalent of 1-lithio-2-octadecylcyclopropene as well as dimerisation of the cyclopropene anion and ring opened products. It was found that an inverse order of addition, adding the generated anion to a large excess of iodide, improved the yields considerably. The 1-iodo-ω-(2-octadecylcyclopropene1-yl)-alkanes were then converted into cyanocyclopropanes by a well-established method [8]. Mild base hydrolysis and immediate esterification of the acid gave methyl 4-(2-octadecylcyclopropene-1-yl)butanoate (**10**) and methyl 5-(2-octadecylcyclopropene-1-yl)-pentanoate (**11**). Both cyclopropene esters were subjected to hydrogenation with palladium on charcoal to give the corresponding *cis*-cyclopropane esters (**12**, **13**). The stereospecificity of the hydrogenated products (**12**, **13**) was confirmed by $^1$H-NMR, which showed signals at δ −0.35 to −0.38 (1H) and 0.54 (3H) characteristic of *cis*-cyclopropane long-chain esters [9]. The carbon-13 signals for the cyclopropene compounds (**4–7**, **10**, **11**, **16**, **22**) were assigned according to the guidelines in a recent review [10]. This has resulted in a reassignment of some of the signals in the previously published spectrum [6] of compound **10**.

In order to synthesise methyl 3-(2-octadecyl-cyclopropene-1-yl)propanoate (**22**) a two-carbon precursor is required for the coupling reaction with tribromocyclopropane (**2**). Ethylene oxide is a possible precursor, but a new procedure allows the oxidation of cyclopropenes by protecting these as diiodocyclopropanes [11] (Scheme 2). It is possible to couple the tribromocyclopropane to THP-protected iodopropanol (**15**). The THP-protected cyclopropene alcohol (**16**) was formed in satisfactory yield (55%) and allowed to react with iodine.




Scheme 1. Synthesis of cyclopropene and cyclopropane fatty acids (**10**, **11**, **12**, **13**).

The reaction had to be followed closely by TLC, as the product (**17**) decomposed under prolonged reaction conditions. A mixture of *cis* and *trans*-diiodocyclopropanes was formed in this reaction, and these were not separated. The carbon-13 spectra of these mixtures were very complex, and further work is needed in order to assign the carbon-13 signals. The THP group was removed under mild conditions to yield the diiodocyclopropane alcohol (**18**). Oxidation with purple benzene led to the formation of the corresponding acid (**19**), which was esterified under phase transfer conditions without isolation [12]. Originally the deprotection of the cyclopropene was carried out by reaction of the diiodocyclopropane with *n*-butyl lithium at −80°C for 5 min [11]. In this case, however, the only two compounds isolated from this reaction were starting material and 1,1-dibutyl-3-(2-octadecylcyclopropen-1-yl)propanol (**21**), formed through a lithium iodine exchange and elimination of lithium bromide followed by attack of butyl lithium on the ester. A method was needed to achieve the elimination of the iodine atoms without affecting the ester group. β-Elimination, as desired here, is often a problem in the formation of organozinc reagents from alkyl iodides or bromides that carry a leaving group in β position [13]. This encouraged us to attempt a




Scheme 2. Synthesis of methyl 3-(2-octadecyl-cyclopropene-1-yl)propanoate (22).

reaction of the diiodocyclopropane with active zinc in order to eliminate zinc iodide after insertion of the activated zinc into one carbon-iodine bond. Many methods have been described to generate active zinc, among which we chose a method where active zinc is formed by the reduction of zinc dichloride with lithium naphthalene [14]. The reaction was carried out on a small scale,

and it was necessary to prepare a larger amount of active zinc, as the preparation of active zinc on a smaller scale and in higher dilution was unsuccessful. One equivalent of active zinc was then reacted with methyl 3-(1,2-diiodo-2-octadecylcyclopropyl)propanoate (**20**) at low temperature, and the reaction was allowed to warm up to room temperature. Following the reaction by TLC, the starting material had completely disappeared after 3 h. The only product isolated was the desired methyl 3-(2-octadecyl-cyclopropene-1-yl)propanoate (**22**) in very good yield (84%). It showed the characteristic singlet at 0.78 in the $^{1}$H-NMR for the protons on C-3 of the cyclopropene ring, peaks at 7.54, 107.61 and 111.18 in the $^{13}$C-NMR for the carbons of the cyclopropene ring and signals at 3.66 and 51.68 for the methyl ester.

All four new compounds are currently being tested as inhibitors of the biosynthesis of mycolic acids, and the results will provide further information about the specificity of the enzyme which has been shown [7] to be inhibited by methyl 4-(2-octadecylcyclopropene-1-yl)butanoate (**10**).

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