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The synthesis of (11*R*,12*S*)-lactobacillic acid and its enantiomer

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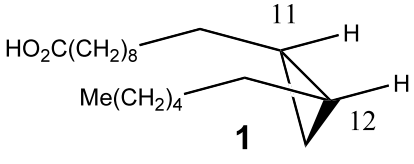
Abstract—(11*R*,12*S*)-Lactobacillic acid has been prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde, in a sequence involving asymmetric cyclopropanation, and from *cis*-cyclopropane-1,2-dimethanol, using enzymatic desymmetrisation. The key step in the former route was the stereochemically controlled cyclopropanation of (1*Z*,4′*S*)-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-octene via a Simmons–Smith type reaction, using diethylzinc and chloroiodomethane. This product was converted into the key intermediate (1*R*,2*S*)-1-formyl-2-hexylcyclopropane, which was also obtained by a known sequence from the (1*R*,2*S*)-monobutyrate ester of *cis*-cyclopropane-1,2-dimethanol. This pivotal aldehyde was converted into (11*R*,12*S*)-lactobacillic acid. Using analogous chemistry, the (11*S*,12*R*)-enantiomer of lactobacillic acid was prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde or from the (1*S*,*R*)-monobutyrate ester of *cis*-cyclopropane-1,2-dimethanol.

1. Introduction

Hofmann and Lucas identified lactobacillic acid[1] in 1950, following studies on the relation between biotin and fatty acids.[2] Saponification of the lipids from *Lactobacillus arabinosus* and *Lactobacillus casei*[3,4] yielded a novel fatty acid of chemical composition $C_{19}H_{36}O_2$ and X-ray diffraction patterns indicated a C_{18} chain length. Failure to react with potassium permanganate, monoperphthalic acid and catalytic hydrogenation to give two methyl branched octadecanoic acids, indicated the presence of a cyclopropane ring. The 11,12 position of the cyclopropane ring was determined by degradative studies.[5,6] Racemic *cis*- and *trans*-11,12-methylene octadecanoic acids were synthesised[7,8] and the infrared spectrum of the *cis*-isomer was identical to that of lactobacillic acid.[8] Subsequently, the absolute configuration of lactobacillic acid **1** was assigned as (11*R*,12*S*) , by comparison with related cyclopropyl ketones;[9] this is reported to have been confirmed.[10]

Previous syntheses of lactobacillic acid and related analogues have given racemic products.[8] It was important to develop an asymmetric synthesis of lactobacillic acid to confirm the absolute configuration of the cyclopropane group. The synthesis of (11*R*,12*S*)-lactobacillic acid **1** involved the key homochiral intermediate aldehyde **10**, obtained by two independent routes (Scheme 1). One route involves diastereoselective Simmons–Smith cyclopropanation of a *cis*-unsaturated protected diol **3**. In the alternative, known, route, stereoselectivity is obtained through enzymatic desymmetrisation of the dibutyrate of *cis*-cyclopropane-1,2-dimethanol to give the intermediate **10**. This pivotal aldehyde **10** was converted by standard chemistry into (11*R*,12*S*)-lactobacillic acid **1** (Scheme 2). Both routes were adapted to



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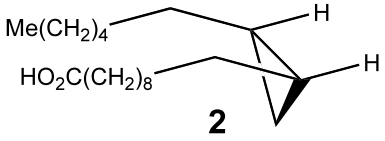

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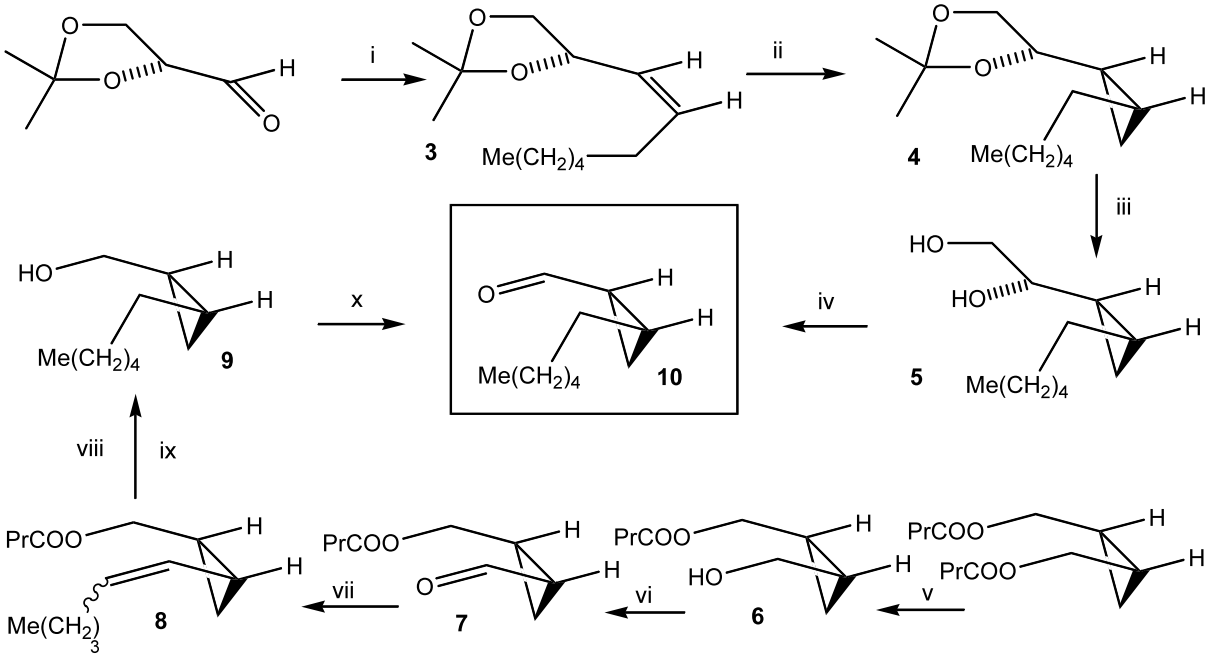
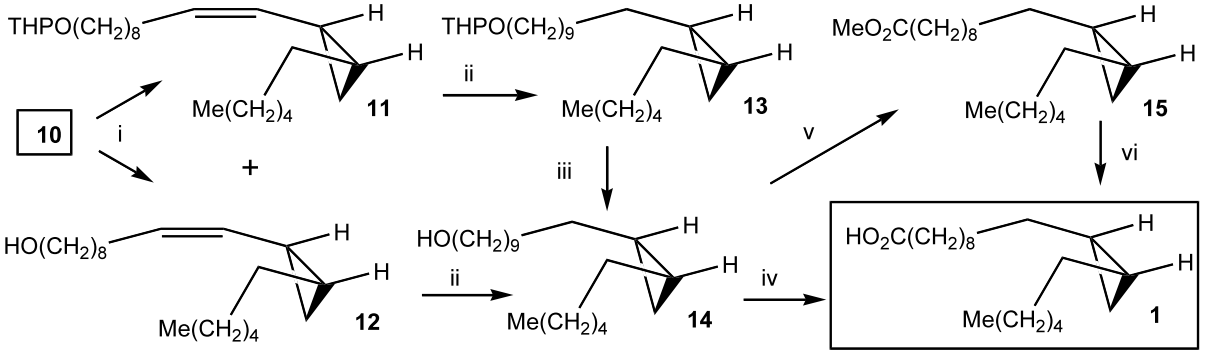


Scheme 1. *Reagents and conditions*: (i) $Br^{-}Ph_3P^{+}(CH_2)_6Me$, *n*-BuLi, THF, −78°C (82%); (ii) Et_2Zn, $ClCH_2I$, 1,2-dichloroethane, −30°C (90%); (iii) HCl, MeOH (80%); (iv) $NaIO_4$, H_2O (57%); (v) pig liver esterase, ethylene glycol, water, pH 6.5 (80%); (vi) PCC, DCM (88%); (vii) $Br^{-}Ph_3P^{+}(CH_2)_4Me$, *t*-BuOK, THF, −78°C (70%); (viii) K_2CO_3, MeOH (98%); (ix) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, *i*-PrOH (87%); (x) PCC, DCM (94%).



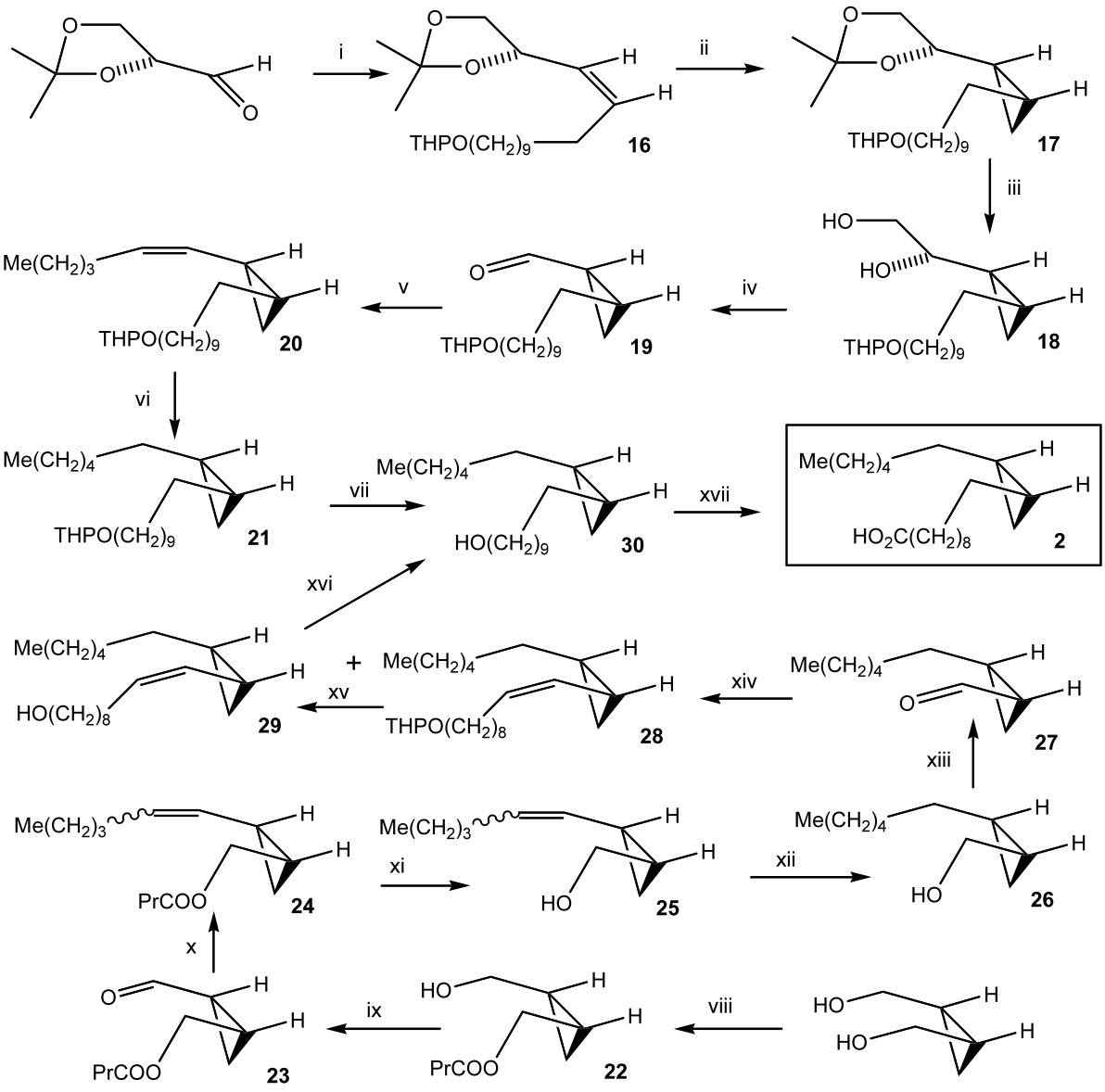
Scheme 2. *Reagents and conditions*: (i) 9-tetrahydropyranyloxynonyltriphenylphosphonium bromide, NaHMDS, THF, −78°C, 11% (THP), 33% (OH); (ii) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, *i*-PrOH, 66% (THP) 80% (OH); (iii) *p*-TSA, DCM 80%; (iv) RuO_2, acetonitrile, MeOH, H_2O, $NaIO_4$, 20%; (v) $KMnO_4$, cetrimide, DCM, H_2O followed by diazomethane, diethyl ether, 64%, (vi) NaOH, H_2O, MeOH, reflux, then aq. HCl, 55%.

provide the 11*S*,12*R* enantiomer **2** of lactobacillic acid (Scheme 3). A preliminary report has been published.[11]

2. Results and discussion

In the first route to the key homochiral intermediate **10** (Scheme 1), Wittig reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde[12] with heptyltriphenylphosphonium bromide gave the desired *cis*-alkene **3**. Enantioselective Simmons–Smith cyclopropanation of **3**, with diethyl zinc and chloroiodomethane,[13,14] yielded the cyclopropane **4** in 90% yield. The (1*R*,2*S*) absolute configuration of **4** was assigned according to previous guidelines[15–17] and subsequent corroboration with the alternative desymmetrisation route (Scheme 1). The zinc carbenoid is considered to coordinate with the isopropylidene ring of the alkene **3**, directing the methylene transfer to the bottom (1*re*,2*si*)-face (Fig. 1).[15–18] Acidic deprotection of **4** gave the diol **5** and subsequent periodate cleavage yielded the formylcyclopropane **10**.

The second route to the homochiral intermediate aldehyde **10** (Scheme 1) involved desymmetrisation of *cis*-1,2-bis(butyroyloxymethyl)cyclopropane with pig liver esterase in ethylene glycol and water at pH 6.5 to give the monoester **6**, according to published procedures.[19,20] Oxidation of **7** with PCC gave the aldehyde **7**, which reacted with *n*-pentyltriphenyl phosphonium bromide and potassium *t*-butoxide in tetrahydrofuran at −78°C to give the unsaturated ester **8** as a mixture of *Z*- and



Scheme 3. *Reagents and conditions*: (i) 11-tetrahydropyranyloxyundecyltriphenyl phosphonium bromide, NaHMDS, THF, –78°C; (ii) Et_2Zn, $ClCH_2I$, 1,2-dichloroethane, –30°C, 87%; (iii) HCl, MeOH, 84%, (iv) $NaIO_4$, H_2O 83%; (v) $Br^{-}Ph_3P^{+}(CH_2)_4Me$, LHMDS, THF, –78°C, 83%; (vi) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, *i*-PrOH, 87%; (vii) *p*-TSA, MeOH, 91%; (viii) $CF_3CH_2OCO(CH_2)_2Me$, pig liver esterase, 81%; (ix) PCC, DCM, 88%; (x) $Br^{-}Ph_3P^{+}(CH_2)_4Me$, *t*-BuOK, THF, –78°C, 70%; (xi) K_2CO_3, MeOH, 98%; (xii) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, *i*-PrOH, 87%; (xiv) PCC, DCM, 94%; (xiv) 9-tetrahydropyranyloxynonyltriphenylphosphonium bromide, *t*-BuOK, THF, –80°C, 21% (THP), 21% (OH); (xv) *p*-TSA, aq. MeOH, 81%; (xvi) N_2H_4, H_2O, $NaIO_4$, CH_3COOH, $CuSO_4$, *i*-PrOH (99%); (xvii) PDC, DMF, DCM, 76%.

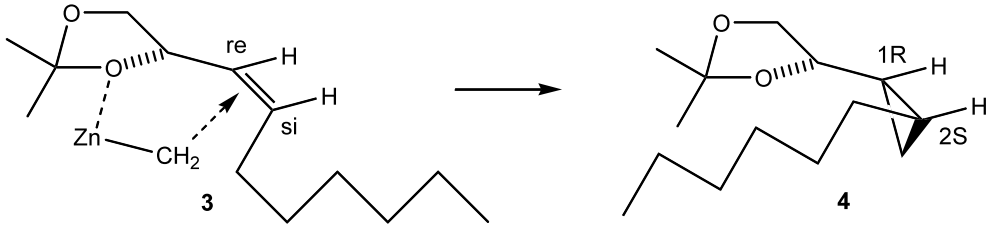


Figure 1. Stereochemical control in cyclopropanation.

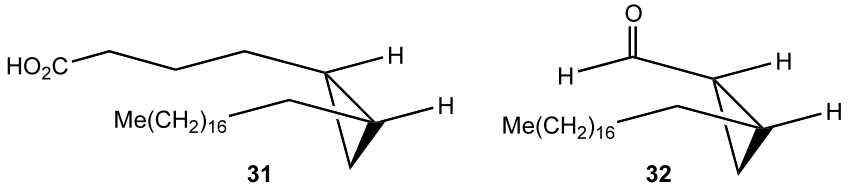
E-isomers (ca. 6:1). More selective formation of *E*- or *Z*-isomers has been reported using either a more complex phosphonium salt or HMPT as solvent,[19] but selectivity was not required here. Methanolic potassium carbonate saponification of **8** and reduction of the product with di-imide,[21,22] generated from hydrazine hydrate, copper sulfate, ethanoic acid and sodium (meta)periodate, at 57°C for 3 h, gave the saturated alcohol **9**. Oxidation of **9** with PCC gave the aldehyde **10**, identical to that prepared by the alternative route (Scheme 1).

The synthesis of (11*R*,12*S*)-lactobacillic acid **1**, from the intermediate aldehyde **10**, was completed as outlined in Scheme 2. 2-(9-Bromononyloxy)tetrahydropyran[23] was kept with triphenyl phosphine in toluene at 120°C for 3 days. The resulting phosphonium salt was treated with sodium (bis)dimethylsilylamide in THF at ambient temperature, followed by addition of the formylcyclopropane **10** at −78°C; this afforded the tetrahydropyranyl ether **11** and the alcohol **12** in 11 and 33% yields, respectively. The selective reduction of the double bonds of the cyclopropanes **11** and **12** with diimide[21,22] gave the saturated products **13** and **14**. The alcohol **14** was also obtained by removal of the tetrahydropyranyl group from **13**, using *p*-toluenesulfonic acid at ambient temperature over 24 h. Subsequent oxidation of the alcohol **14** with sodium (meta)periodate, ruthenium dioxide and potassium carbonate in methanol, water and acetonitrile yielded lactobacillic acid **1**, in 20% yield and with a specific rotation of +0.16, in agreement with literature.[24] Alternatively, the methyl ester **15** of **1** was obtained after oxidation of **14** with potassium permanganate and cetrimide in acetonitrile and water followed by treatment with diazomethane with an overall yield of 62%. Saponification of **15** with aqueous NaOH and methanol afforded **1**, as above.

The alternative (11*S*,12*R*)-enantiomer **2** of lactobacillic acid was synthesised either from 2,3-*O*-isopropylidene-D-glyceraldehyde or from the key formyl cyclopropane **23** (Scheme 3). The former route involved chemistry analogous to that shown in Schemes 1 and 2, with reversed addition of the two chains. The Wittig reagent, prepared from 2-(11-bromoundecyloxy)-tetrahydropyran[25] reacted with 2,3-*O*-isopropylidene-D-glyceraldehyde,[12] to generate the *cis* alkene **16** with 100% d.e. (Scheme 3). Cyclopropanation of **16**, using chloroiodomethane and diethylzinc, afforded the cyclopropane **17**. Stereoselectivity was again assigned as 11*R*,12*S*, according to previous guidelines.[15–17] Following standard transformations, via **18** and **19**, a second Wittig reaction afforded the alkene **20** which was selectively reduced with diimide to give the saturated product **21**. Deprotection of the THP ether from **21** gave the cyclopropane alcohol **30**.

In the alternative route to intermediate **30** (Scheme 3), the key stage was the desymmetrisation of *cis*-cyclopropane-1,2-dimethanol. A freshly prepared solution of 2,2,2-trifluoroethyl butyrate in isopropyl ether was mixed with *cis*-1,2-bis(hydroxymethyl)-cyclopropane in THF and stirred for 48 h in the presence of pig liver esterase to produce the half-ester **22**. Oxidation of **22** to the intermediate aldehyde **23** was followed by Wittig reaction to produce the unsaturated ester **24**, which was hydrolysed with K_2CO_3 to give **25**. Saturation of **25** gave **26**, whose optical purity was established, along with that of compound **9** (Scheme 1), by Mosher derivatisation. The alcohol **26** was oxidised to the aldehyde **27**. Reaction of **27** with a THP-protected phosphonium salt gave a mixture of a THP intermediate **28** and the corresponding alcohol **29**; deprotection of **28** gave additional **29**. Saturation of **29** gave **30**, identical to that produced by the route above (Scheme 3). Oxidation of the alcohol **30**, with PDC, gave the (11*S*,12*R*)-lactobacillic acid enantiomer **2**; the methyl ester of **2** was also prepared.

In a related study, diastereoselective cyclopropanation of an alkene derived from 2,3-*O*-isopropylidene-D-glyc-



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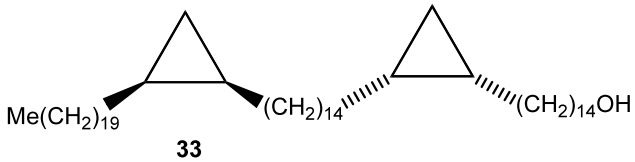

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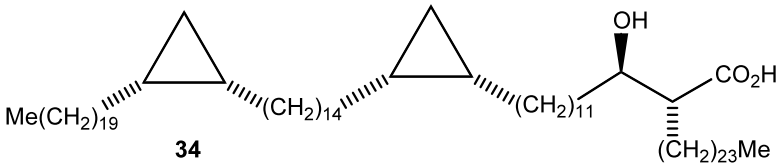

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eraldehyde has been used to prepare long-chain cyclopropanes.[26] (1*S*,2*R*)-1-Acetoxymethyl-2-hydroxymethylcyclopropane has also recently been applied in the syntheses of other cyclopropane fatty acids.[27] Versatile 2 - (*t* - butyldiphenylsilyloxy)methyl - 1 - formylcyclopropanes have been developed as synthons leading to homochiral *cis*- and *trans*-1,2-disubstituted cyclopropanes.[28] Homochiral *endo*-methylene nucleosides have been prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde.[17]

In our preliminary communication,[11] we reported the synthesis of **31**, a possible precursor of so-called α-mycolic acids from *Mycobacterium tuberculosis*, via the intermediate **32**. Subsequent studies[29] have reported the synthesis of the 'meromycolic' acid portion **33** with the aim of developing the first total chiral synthesis of an enantiomer of a natural mycolic acid, such as **34**. The availability of routes to configurationally defined cyclopropane intermediates is of great value in defining precise biosynthetic pathways leading to mycolic acids, especially as key cyclopropanation enzymes have been characterised recently.[30]

3. Conclusion

Two general routes for the synthesis of single enantiomers of long-chain cyclopropane fatty acids have been developed for the preparation of lactobacillic acid **1** and its enantiomer **2**. These syntheses confirm that natural lactobacillic acid has the (11*R*,12*S*) absolute configuration. In the preliminary account of this work,[11] it was mistakenly stated that the intermediate ester **7** was produced by enzyme catalysed desymmetrisation of *cis*-cyclopropane-1,2-dimethanol (see Scheme 3); in fact, it was produced by enzyme-catalysed desymmetrisation of the dibutyrate ester of the diol, as shown in Scheme 1.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded on Brucker AC 200, AC 250 CP/MAS or JEOL λ500 NMR spectrometers in $CDCl_3$. IR spectra were recorded using Nicolet FTIR PCIR or Perkin–Elmer 1600 FTIR infrared spectrophotometers for liquid films. Electron impact (EI) mass spectra (MS) were recorded using either a Kratos MS 80RF or Micromass Auto Spec M spectrometer. GC analysis was carried out on a Perkin–Elmer 8410 gas chromatograph, equipped with an OV1 capillary column (50 m). Optical rotations were achieved using an Optical Activity POLAAR 2001 automatic polarimeter. Melting points (uncorrected) were carried out on a Kofler hot stage apparatus. Thin-layer chromatography was performed using Fluka 60763 glass backed plates and Fluka 70643 aluminium-backed TLC cards; separated components were detected by spraying with 10% ethanolic molybdophosphoric acid followed by charring. Flash column chromatography was performed at medium pressure using Fluka 60738 silica gel 60. Starting materials and chemical reagents were all purchased from Aldrich, Fluka or Lancaster Synthesis. Pig liver esterase was obtained from Sigma. Petrol refers to low-boiling petroleum ether (bp 40–60°C). Solutions in organic solvents were dried over anhydrous magnesium sulfate.

4.1. (1*Z*,4′*S*)-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-1-octene 3

n-Heptyltriphenylphosphonium bromide (39 g, 88 mmol) was dissolved in anhydrous THF (400 mL), under nitrogen, and cooled to −78°C. *n*-Butyllithium in hexanes (51 mL, 128 mmol) was added, with stirring, and the reaction warmed to ambient temperature for 10 min before being re-cooled to −78°C followed by the addition of 2,3-*O*-isopropylidene-D-glyceraldehyde (10.5 g, 80 mmol). The reaction was stirred between −10 and 0°C for 2 h and 10% aq. ammonium chloride was added (50 mL) to quench the reaction. The mixture was extracted with dichloromethane (2×50 mL), the organic phase washed with water (50 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography, using petrol and diethyl ether in a ratio of 5:2, to yield **3** (13.9 g, 82%) as a colourless oil. IR (film) 3097, 2985, 2921, 2852, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.64 (dt, CH, 1H, *J* 10.9, 7.5 Hz), 5.41 (dd, CH, 1H, *J* 10.9, 8.6 Hz), 4.81 (q, CH, 1H, *J* 7.5 Hz), 4.02 (dd, CH, 1H, *J* 8.0, 6.0 Hz), 3.50 (t, CH, 1H, *J* 8.0 Hz), 2.16 (p, CH_2, 2H, *J* 6.4 Hz), 1.41 (s, Me, 3H), 1.39 (s, Me, 3H), 1.26 (br.s, C_4H_8, 8H), 0.87 (t, CH_3, 3H, *J* 7 Hz); ^{13}C NMR ($CDCl_3$) δ 135.2 (CH), 127.0 (CH), 108.9, 72.0, 69.4, 31.6, 29.7, 29.6, 26.9, 25.9, 22.6, 22.3, 14.1; EI MS *m*/*z* 212.1764 (M$^+$); $[\alpha]_D^{24} = +67.3$ (*c* 4.6, $CHCl_3$).

4.2. (1*R*,2*S*,4′*S*)-1-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-2-hexylcyclopropane 4

(1*Z*,4′*S*)-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-1-octene **3** (5.0 g, 23.5 mmol) was dissolved in anhydrous 1,2-dichloroethane (100 mL) and the solution was stirred under nitrogen and cooled to −30°C. Diethyl zinc (42.7 mL, 47 mmol) was added followed by chloroiodomethane (16.6 g, 94 mmol). The solution was warmed to 0°C and stirred for 1 h, whilst being monitored by GC. The reaction was quenched with 10% aq. ammonium chloride (50 mL), extracted with chloroform (2×40 mL) and the combined organic phases washed with water (50 mL), dried and concentrated in vacuo. The residue was purified by flash chromatography, eluting with petrol:diethyl ether (5:2), to yield the product **4** (4.8 g, 90%) as a pale yellow oil. IR (film) 3047, 2986, 2957, 2928, 2871, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.10 (q, CH, 1H, *J* 4.1 Hz), 3.68 (m, CH_2, 2H), 1.39 (s, Me, 3H), 1.30 (s, Me, 3H), 1.14 (br.s, C_4H_8, 8H), 1.12 (m, CH_2, 2H), 0.89 (m, CH_3, 6H), 0.18 (m, CH, 1H); ^{13}C NMR ($CDCl_3$) δ 108.9, 78.0, 69.5, 34.1, 31.8, 30.6, 26.8, 25.9, 25.7, 22.1, 15.4, 14.7, 14.1, 10.9; EI MS, *m*/*z* 226.1929 (M$^+$); $[\alpha]_D^{24} = +19.6$ (*c* 0.55, $CHCl_3$).

4.3. (1*R*,2*S*,1′*S*)-1-(1′,2′-Dihydroxyeth-1′-yl)-2-hexylcyclopropane 5

Concentrated aq. HCl (0.5 mL) was added to (1*R*,2*S*,4′*S*)-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-hexylcyclopropane **4** (4.5 g, 20 mmol) in methanol (30 mL) at ambient temperature. The solution was stirred for 2 h, with

monitoring by TLC until no starting material was present. The methanol and residual HCl were removed in vacuo and the residue purified by flash chromatography, using petrol:diethyl ether (1:1) as eluent, to yield **5** (3.0 g, 80%) as a colourless oil. IR (film) 3370, 3065, 2994, 2956, 2935, 1652, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.61 (m, CH, 1H), 3.42 (t, CH, 1H, J 7.6 Hz), 3.19 (m, CH, 1H), 2.70 (br.s, OH, 1H), 2.62 (br.s, OH, 1H), 1.18 (m, C_5H_{10}, 10H), 0.71 (m, 3×CH, CH_3, 6H), 0.0 (m, CH, 1H); ^{13}C NMR ($CDCl_3$) δ 73.3 (COH), 67.0 (COH), 31.8, 30.0, 29.2, 22.6, 18.5, 13.4, 12.6, 9.5; EI MS m/z 186.1610 (M^+); $[\alpha]_D^{24}=+21.9$ (c 0.21, $CHCl_3$).

4.4. (1*R*,2*S*)-1-Butyroyloxymethyl-2-hydroxymethylcyclopropane 6, (1*R*,2*S*)-1-butryloxymethyl-2-formylcyclopropane 7, *Z*- and *E*-(1*R*, 2*S*)-1-butyryloxymethyl-2-(hex-1-en-1-yl)cyclopropanes 8 and (1*R*,2*S*)-2-hexyl-1-hydroxymethylcyclopropane 9

(1*R*,2*S*) - 1 - Butryloxymethyl - 2 - hydroxymethylcyclopropane **6** was prepared by desymmetrisation of *cis*-cyclopropane-1,2-dimethanol, dibutyl ester, according to a published procedure;[20] compound **6** showed $[\alpha]_D^{24}=+19.8$ (c 2.8, $CHCl_3$) (lit.:[20] $[\alpha]_D^{24}=+18.2$ (CH_2Cl_2)) and had IR and NMR as for **22**, below. Compound **6** was converted into (1*R*,2*S*)-1-butryloxymethyl-2-formylcyclopropane **7**, as published;[20] the ^1H and ^{13}C spectra were identical to those for the enantiomer **23**, below, with $[\alpha]_D^{24}=+88.9$ (c 2.14, $CHCl_3$) (lit.:[20] $[\alpha]_D^{24}=+59.8$ (CH_2Cl_2)). Wittig reaction of **7**, as for compound **23** (see later), gave a mixture of *Z*- and *E*-(1*R*,2*R*)-1-butyroyloxymethyl-2-(hex-1-en-1-yl)cyclopropanes **8** (ca. 6:1), essentially identical by NMR to the mixture of compounds **24** (see later) and containing all the peaks reported for the two separate isomers.[27] Hydrolysis of **8** was followed by reduction with diimide to produce **9** (86%), as described in detail later for the transformation of **24** to **26**, via **25**. Compound **9** was identical by IR and NMR to **26**, below, but showed $[\alpha]_D^{24}=+23.1$ (c 1.8, $CHCl_3$).

4.5. (1*R*, 2*S*)-1-Formyl-2-hexylcyclopropane 10

(a) (1*R*,2*S*,1′*S*)-1-(1′,2′-Dihydroxyeth-1′-yl)-2-hexylcyclopropane **5** (0.22 g, 1.0 equiv., 0.9 mmol) was dissolved in methanol (20 mL) and the solution cooled to 0°C. Sodium periodate (3.9 g, 1.2 equiv., 18 mmol) in distilled water (10 mL) was added and the mixture stirred; when TLC indicated the completion of the reaction (20 min), 10% aq. ammonium chloride (20 mL) was added. The resulting mixture was extracted with dichloromethane (2×40 mL), dried, concentrated in vacuo and purified by flash chromatography, using petrol:diethyl ether (2:1) ratio as eluent, to yield the product **10** (1.3 g, 57%) as a pale yellow oil; $[\alpha]_D^{24}=+23.6$ (c 0.12, $CHCl_3$). This was identical by ^1H and ^{13}C NMR to the compound prepared independently by oxidation of (1*R*, 2*S*)-2-hexyl-1-hydroxymethylcyclopropane **9**, below.

(b) (1*R*,2*S*)-2-Hexyl-1-hydroxymethylcyclopropane **9** was oxidised by the method described later, for its enantiomer **26**, to give **10** whose spectroscopic data was identical to that obtained later for **26**, except for $[\alpha]_D^{24}=+16.4$ (c 1.3, $CHCl_3$).

4.6. (1′*Z*,1*R*,2*S*)-2-Hexyl-1-[[(10′-tetrahydropyranyl)-oxy]dec-1′-en-1′-yl]cyclopropane 11 and (1′*Z*, 1*R*, 2*S*)-2-Hexyl-1-(10′-hydroxydec-1′-en-1′-yl)cyclopropane 12

Triphenylphosphine (26.0 g, 99 mmol) and 2-(9-bromononyloxy)-tetrahydropyran[23] (28.0 g, 90 mmol) were dissolved in toluene (250 mL) and the solution refluxed for 3 days. The mixture was reduced in vacuo to remove the toluene and the residue washed with petrol (3×100 mL) to give crude 1-tetrahydropyranyl-9-nonyltriphenylphosphonium bromide (48.3 g, 94%), as a dark brown oil. The crude phosphonium salt (6.1 g, 9.7 mmol), dissolved in anhydrous THF (200 mL), was stirred under an atmosphere of nitrogen at ambient temperature and sodium bis(trimethylsilyl) amide (9.7 mL, 19.4 mmol) added. The mixture was stirred for a further 10 min cooled to −78°C and (1*R*,2*S*)-1-formyl-2-hexylcyclopropane **10** (1.5 g, 9.7 mmol) added. The reaction was allowed to stir for 2 h at ambient temperature before being quenched with 10% aq. ammonium chloride (20 mL). The reaction mixture was extracted with dichloromethane (2×50 mL) and the organic phase washed with water (50 mL), dried and reduced in vacuo. TLC analysis, eluting with 5:1 petrol:diethyl ether, showed two spots, R_f 0.97 and 0.48, which were purified by flash chromatography, using petrol:diethyl ether (5:2) as eluent, to yield the products **11** (124 mg, 11%) and **12** (382 mg, 33%), as colourless oils.

Compound 11 showed: IR (film) 3054, 3023, 3020, 2997, 1732, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (dt, CH, 1H, J 10.8, 6.8 Hz), 5.05 (t, CH, 1H, J 10.8 Hz), 4.51 (t, CH, 1H, J 2.7 Hz), 3.91–3.51 (m, CH_2, 2H), 3.12–3.48 (m, CH_2, 2H), 2.01 (m, CH_2, 2H), 1.62 (m, CH_2, 2H), 1.58–1.12 (m, 10×CH_2, C_3H_6, 26H), 0.89 (t, CH_3, 3×CH, 6H, J 5.6 Hz), 0.01 (m, CH, 1H); ^{13}C NMR ($CDCl_3$) δ 130.2 (CH), 129.5 (CH), 98.9, (OCO), 67.7 (COTHP), 62.3 (COC), 31.9, 30.8,29.8, 29.7, 29.5, 29.3, 29.2, 27.5, 26.3, 25.5, 22.7, 19.7, 18.5, 14.2, 14.1, 13.9; EI MS m/z 364.3345 (M^+); $[\alpha]_D^{24}=+36.8$ (c 0.06, $CHCl_3$).

Compound 12 showed: IR (film) 3339, 3063, 2992, 2925, 1420, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (dt, CH, 1H, J 10.8, 7.3 Hz), 4.90 (t, CH, 1H, J 10.8 Hz), 3.53 (t, CH_2, 2H, J 6.4 Hz), 2.05 (m, CH_2, 2H), 1.98 (brm, OH, 1H), 1.18 (s, $C_{11}H_{22}$, 22H), 0.89 (t, 3×CH, CH_3, 6H, J 5.6 Hz), 0.01 (m, CH, 1H); ^{13}C NMR ($CDCl_3$) δ 130.1 (CH), 129.4 (CH), 63.0 (COH), 32.7, 31.8, 29.7, 29.6, 29.4, 29.3, 29.2, 27.4, 26.8, 25.7, 22.6, 18.4, 14.1, 14.1, 14.0, 13.8; EI MS m/z 280.2764 (M^+); $[\alpha]_D^{24}=+9.7$ (c 0.76, $CHCl_3$).

4.7. (1*R*,2*S*)-2-Hexyl-1-[[(10′-tetrahydropyranyl)oxy]dec-1′-yl]cyclopropane 13

Sodium periodate (1.75 g, 8.2 mmol) in water (10 mL) was added dropwise over 2 h to a stirred mixture of (1′*Z*,1*R*,2*S*)-2-hexyl-1-[[(10′-tetrahydropyranyl)oxy]dec-

1′-en-1′-yl]cyclopropane **11** (0.3 g, 0.82 mmol), hydrazine hydrate (0.65 mL), ethanoic acid (0.5 mL) and satd aq. copper sulfate (0.5 mL), dissolved in isopropanol (10 mL). The reaction mixture was stirred for 3 days before being quenched with 10% aq. ammonium chloride (20 mL, w/v). The mixture was extracted with dichloromethane (2×50 mL), washed with water (2×20 mL) and dried. The organic phase was reduced in vacuo and the residue purified by flash chromatography, using petrol:ethyl acetate (8:1) as eluent, to yield **13** (200 mg, 66%) as a pale red oil. IR (film) 3058, 2954, 2924, 2853, 1465, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.61 (m, CH, 1H), 3.62 (t, CH_2, 2H, J 6.5 Hz), 3.54 (t, CH, 1H, J 6.7 Hz), 3.38 (t, CH, 2H, J 6.6 Hz), 1.62 (m, CH_2, 2H), 1.45 (m, 2×CH_2, 4H), 1.34 (m, C_3H_6, C_6H_{12}, C_8H_{16}, 30H), 0.92 (t, CH_3, 3H, J 5.6 Hz), 0.67 (m, 3×CH, 3H), –0.31 (m, CH, 1H); ^{13}C NMR ($CDCl_3$) δ 98.9 (OCO), 70.1 (COTHP), 67.7 (COC), 32.7, 32.0, 31.7, 30.8, 30.2, 29.7, 29.6, 29.5, 29.4, 29.3, 28.9, 28.7, 28.5, 27.9, 27.4, 26.9, 26.2, 25.5, 25.1, 19.7, 16.1, 15.5, 14.1, 10.9; $[\alpha]_D^{24}$ = +6.0 (c 0.06, $CHCl_3$).

4.8. (1*R*,2*S*)-2-Hexyl-1-(10′-hydroxydec-1′-yl)cyclopropane 14

(a) *p*-Toluenesulfonic acid (100 mg) was added to a stirred solution of (1*R*,2*S*)-2-hexyl-1-[[(10′-tetrahydropyranyl)-oxy]dec-1′-yl]cyclopropane **13** (300 mg, 3.2 mmol) dissolved in dichloromethane (20 mL). The reaction mixture was stirred at ambient temperature for 24 h when TLC showed no starting material. The mixture was filtered, reduced in vacuo and the residue purified by flash chromatography, using petrol:diethyl ether (2:1), to yield **14** (200 mg, 80%) as a colourless oil.

(b) Sodium (meta)periodate (6.8 g, 32 mmol) in water (10 mL) was added dropwise to a stirred solution of (2′*Z*,1*R*,2*S*)-2-hexyl-1-(10′-hydroxydec-2′-en-1′-yl)cyclopropane **12** (300 mg, 3.2 mmol), hydrazine hydrate (1.95 mL), ethanoic acid (0.5 mL) and satd aq. copper sulfate (0.5 mL) in isopropanol (20 mL) over 2 h at 50°C. The reaction was stirred for 3 days before being quenched with 10% aq. ammonium chloride (20 mL). The organic phase was extracted with dichloromethane (2×50 mL), washed with water (2×20 mL) and dried. The organic phase was reduced in vacuo and the residue purified by flash chromatography eluting with petrol:ethyl acetate (8:1) to yield **14** (170 mg, 58%). IR (film) 3409, 3057, 2925, 2853, 1299 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (t, CH_2, 2H, J 6.5 Hz), 2.52 (brs, OH, 1H), 1.55 (m, 2×CH_2, 4H), 1.31 (brs, $C_{12}H_{24}$, 24H), 0.92 (t, CH_3, 3H), 0.72 (m, 3×CH, 3H), –0.31 (m, CH, 1H); ^{13}C NMR ($CDCl_3$) δ 63.1 (COH), 32.8, 32.0, 31.9, 30.2, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 26.2, 25.7, 22.7, 18.7, 18.5, 15.8, 13.9, 10.9; EI MS m/z 282.2922 (M^+); $[\alpha]_D^{24}$ = +11.0 (c 0.35, $CHCl_3$).

4.9. Methyl lactobacillate 15

(1*R*,2*S*)-1-Hexyl-2-(10′-hydroxydec-1′-yl)cyclopropane **14** was converted to methyl lactobacillate **15** (64%), as described later for its enantiomer (see Section 4.26); spectroscopic data were identical for these two enantiomers.

4.10. (1*R*,2*S*)-1-(9′-Carboxynon-1′-yl)-2-hexylcyclopropane or (11*R*,12*S*)-lactobacillic acid 1

(a) (1*R*,2*S*)-2-Hexyl-1-(10′-hydroxydec-1′-yl)cyclopropane **14** (200 mg, 0.69 mmol) was dissolved in a solution of methanol (20 mL), acetonitrile (20 mL) and water (30 mL). Sodium periodate (600 mg, 2.8 mmol) and ruthenium dioxide (100 mg) were added and the reaction mixture stirred overnight at 80°C. The mixture was filtered through Celite, dried and reduced in vacuo. The crude residue was purified by flash chromatography, using petrol:ethyl acetate (8:1) as eluent, to yield **1** (40 mg, 20%) as a pale yellow oil.

(b) (11*R*,12*S*)-Methyl lactobacillate (450 mg, 5.1 mmol) **15** was dissolved in methanol (20 mL) and aqueous sodium hydroxide solution (10%) (10 mL) added. The mixture was heated and stirred for 18 hours before acidifying with aq. HCl (10%) (15 mL). The solution was washed with dichloromethane (3×20 mL), the organic fractions collected, dried and reduced under vacuum. The crude mixture was purified by flash chromatography, using petrol:diethyl ether (5:2) as eluent, to give **1** (240 mg, 55%) as a colourless oil. IR (film) 3480–3200, 3057, 2988, 2925, 2854, 1653 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (t, CH_2, 2H, J 7.3 Hz), 1.61 (m, 2×CH_2, 4H), 1.29–1.04 (m, C_7H_{14}, C_4H_8, 22H), 0.89 (t, CH_3, 3H, J 5.6 Hz), 0.56 (m, 3×CH, 3H), –0.34 (q, CH, 1H, J 3.8 Hz); ^{13}C NMR ($CDCl_3$) δ 180.0 (COOH), 54.0, 41.4, 31.9, 29.7, 29.6, 19.5, 29.4, 29.3, 26.9, 24.7, 23.5, 22.7, 22.6, 22.3, 15.7, 14.1, 10.9; EI MS m/z 296.2737 (M^+); $[\alpha]_D^{24}$ = +0.16 (c 0.15, $CHCl_3$), (lit. +0.25).[21]

4.11. (1*Z*,4′*S*)-2-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-1-[[(10″-tetrahydropyranyl)oxy]-decyl]ethene 16

Triphenylphosphine (3.96 g, 15.1 mmol) was added to a solution of 2-(11-bromoundecyloxy)-tetrahydropyran[25] (5.0 g, 13.7 mmol) in toluene (50 mL). The solution was refluxed for 3 days, reduced in vacuo and washed with petrol to yield 1-tetrahydropyranyloxyundecyl-11-triphenylphosphonium bromide (7.8 g, 95%), as a white solid. Sodium (bis)trimethylsilylamide (9.2 mL, 18.4 mmol) was added to a stirring solution of the phosphonium salt (7.6 g, 12.6 mmol) in anhydrous THF (50 mL) at ambient temperature. After 10 min, the solution was cooled to −78°C and 2,3-*O*-isopropylidene-D-glyceraldehyde (1.5 g, 11.5 mmol), in anhydrous THF (10 mL), was added. The mixture was warmed to ambient temperature and stirred for 2 h before being quenched with 10% aq. ammonium chloride (20 mL), and extracted with dichloromethane (2×50 mL). The combined organic phases were dried and reduced in vacuo. The crude product was purified by flash chromatography (petrol:diethyl ether 5:2) to give **16** (2.4 g, 57%) as a pale yellow oil. IR (film) 3089, 2895, 2812, 1410, 1085, 1038, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.50 (dt, CH, 1H, J 11.1, 6.7 Hz), 5.39 (t, CH, 1H, J 11.1 Hz), 4.71 (q, CH, 1H, J 6.2 Hz), 4.42 (m, CH, 1H), 3.92 (dd, CH, 1H, J 8.0, 5.9 Hz), 3.39 (t, CH, 1H, J 8.0 Hz), 3.31 (t, CH_2, 2H, J 6.9 Hz), 3.27 (m, CH_2, 2H), 1.99 (m, 2×CH, 2H) 1.46 (m, C_3H_6, 6H), 1.31 (s, Me, 3H), 1.29 (s. Me, 3H), 1.19 (brs, C_8H_{16}, 16H); ^{13}C NMR ($CDCl_3$) δ 135.1 (CH), 127.1

(CH), 108.9, 72.1 (OCO), 71.8, 70.1 (COTHP), 69.9, 69.5 (COC), 32.7, 29.8, 29.6, 29.5, 29.5, 29.4, 29.2, 27.7, 26.8, 26.2, 26.0, 25.8.; EI MS m/z 368. 2928 (M^+); $[\alpha]_D^{24} = +32.6$ (c 1.27, $CHCl_3$).

4.12. (1*S*,2*R*,4′S)-2-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-1-[[(10″-tetrahydropyranyl)oxy]decyl]cyclopropane 17

(1*Z*,4′*S*)-2-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-1-[[(10″-tetrahydropyranyl)oxy]-decyl]ethene **16** (2.0 g, 5.43 mmol) was dissolved in anhydrous 1,2-dichloroethane (50 mL), stirred under an atmosphere of nitrogen and cooled to −30°C. Diethyl zinc (9.88 mL, 10.8 mmol) was added, followed by chloroiodomethane (3.83 g, 21.6 mmol), the solution warmed to 0°C and stirred for 4 h. The reaction was quenched with 10% aq. ammonium chloride (20 mL), the organic phase extracted with chloroform (3×20 mL) and the combined organic phases washed with water (100 mL). The organic phases were collected, dried, concentrated in vacuo and the residue purified by flash chromatography, using petrol:diethyl ether (5:2), to yield the product **17** (1.74 g, 87%) as a yellow oil. IR (film) 3059, 2987, 2876, 1410 1089 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.42 (m, cH, 1H), 3.98 (m, 2×CH, 2H), 3.39–3.11 (m, 2×CH_2, CH, 5H), 3.11 (t, CH, 1H, J 6.3 Hz), 2.10 (brs, CH_2, 2H), 1.26 (m, C_3H_6, 6H), 1.18 (s, Me, 3H), 1.08 (s, Me, 3H), 1.06 (m, C_8H_{16}, 16H), 0.60 (m, 3×CH, 3H), 0.0 (m, CH, 1H).; ^{13}C NMR ($CDCl_3$): δ 108.4, 78.1 (OCO), 70.1 (COTHP), 69.7 (COC), 62.9, 60.4 (COC), 32.8, 30.0, 29.8, 29.6, 29.5, 29.4, 29.3, 26.9, 26.2, 25.8, 25.7, 21.0, 18.1, 15.4, 14.2, 10.6; EI MS m/z 382. 3079 (M^+); $[\alpha]_D^{24} = +26.2$ (c 2.31, $CHCl_3$).

4.13. (1*S*,2*R*,1′S)-2-(1′,2′-Dihydroxyeth-1′-yl)-1-[[(10″-tetrahydropyranyl)oxy]decyl]cyclopropane 18

Aqueous HCl (10%, 2.0 mL) was added to (1*S*,2*R*,4′S)-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-1-[[(10″-tetrahydropyranyl)oxy]decyl]cyclopropane **17** (1.2 g, 3.15 mmol) in methanol (20 mL). The mixture was stirred at ambient temperature for 4 h until TLC showed that no starting material was present. The methanol was removed in vacuo and the residue purified by flash chromatography, using petrol:diethyl ether (1:1) as eluent, to yield **18** (900 mg, 84%) as a pale yellow oil. IR (film) 3326, 3056, 2987, 2980, 1457 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.42 (m, CH, 1H), 3.62–3.11 (m, 3×CH_2, CH, 7H), 1.87 (brs, 2×OH, CH_2, 2H), 1.31 (m, C_3H_6, 6H), 1.19 (s, C_8H_{16}, 16H), 0.46 (m, 3×CH, 3H), 0.0 (q, CH, 1H, J 3.8 Hz); ^{13}C NMR ($CDCl_3$): δ 73.2 (OCO), 72.1 (COC), 67.1 (COH), 65.6 (COTHP), 63.1 (COH), 32.8, 30.0, 29.5, 26.2, 25.7, 18.7, 16.4, 9.5; EI MS m/z 342. 2778 (M^+); $[\alpha]_D^{24} = -13.2$ (c 2.13, $CHCl_3$).

4.14. (1*S*,2*R*)-2-Formyl-1-[[(10′-tetrahydropyranyl)oxy]-decyl]cyclopropane 19

(1*S*,2*R*,1′S)-2-(1′,2′-Dihydroxyeth-1′-yl)-1-[[(10″-tetrahydropyranyl)oxy]decyl]cyclopropane **18** (800 mg, 2.35 mmol), dissolved in methanol (10 mL), was cooled to 0°C and sodium periodate (74 mg, 2.56 mmol), dissolved in water (10 mL) added. The mixture was stirred for 3 h and quenched with 10% aq. ammonium chloride (20 mL). The mixture was extracted with dichloromethane (2×50 mL), dried, concentrated in vacuo and purified by flash chromatography, using petrol:diethyl ether (2:1), to yield the product **19** (600 mg, 83%) as a yellow oil. IR (film) 3067, 2894, 2977, 1789, 1056 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.07 (d, CHO, 1H, 5.6 Hz), 4.16 (m, CH, 1H), 3.61 (m, CH, 1H), 3.25 (m, CH, 1H), 3.08 (t, CH_2, 2H, J 7.3 Hz), 1.52 (m, CH_2, 2H), 1.21 (m, C_3H_6, 6H), 1.01 (s, C_8H_{16}, 4×CH, 20H); ^{13}C NMR ($CDCl_3$): δ 201.9 (CHO), 102.65, (OCO), 70.9 (COTHP), 66.0 (COC), 65.6 (COC), 41.0, 35.6, 30.9, 29.9, 29.8, 29.2, 27.8, 25.7, 14.8.; EI MS m/z 310. 2509 (M^+); $[\alpha]_D^{24} = +45.1$ (c 1.69, $CHCl_3$).

4.15. (1′*Z*,1*S*,2*R*)-2-(Hex-1′-en-1′-yl)-1-[[(10″-tetrahydropyranyl)oxy]decyl]cyclopropane 20

n-Pentyltriphenylphosphonium bromide (87.8 mg, 2.12 mmol) was suspended in anhydrous THF (50 mL) and LHMDS (3.08 mL, 3.08 mmol) added. The mixture was stirred for 10 min at ambient temperature before being cooled to −78°C and (1*S*,2*R*)-2-formyl-1-[[(10′-tetrahydropyranyl)oxy]decyl]cyclopropane **19** (600 mg, 1.92 mmol) added. The mixture was warmed to ambient temperature and stirred for 2 h before being quenched with 10% aq. ammonium chloride (30 mL). The mixture was extracted with dichloromethane (2×40 mL), dried and reduced in vacuo. The crude residue was purified by flash chromatography, eluting with petrol:ethyl acetate (6:1), to yield **20** (580 mg, 83%) as a pale orange oil. IR (film) 3067, 3054, 2894, 2789, 1090, 1032, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.35 (dt, CH, 1H, J 10.8, 7.9 Hz), 4.91 (t, CH, 1H, J 10.8), 4.36 (m, CH, 1H), 3.71–3.12 (m, 2×CH_2, 4H), 1.61–1.22 (m, 2×CH_2, C_3H_6, 10H), 1.18 (m, C_8H_{16}, C_2H_4, 20H), 1.09–0.86 (m, CH_3, 3×CH, 6H), 0.01 (m, CH, 1H); ^{13}C NMR ($CDCl_3$): δ 133.9 (CH), 129.5 (CH), 102.8 (OCO), 66.0 (COTHP), 63.1 (COC), 38.6, 34.1, 33.6, 32.8, 32.0, 30.4, 29.9, 29.7, 29.5, 27.3, 26.3, 25.8, 15.8, 14.0, 13.9.; EI MS m/z 364.3347 (M^+); $[\alpha]_D^{24} = +23.1$ (c 1.27, $CHCl_3$).

4.16. (1*S*,2*R*)-2-Hexyl-1-[[(10′-tetrahydropyranyl)oxy]-decyl]cyclopropane 21

Sodium periodate (1.2 g, 24.2 mmol) dissolved in water (15 mL) was added dropwise through a dropping funnel, over 30 min, to a stirred mixture of (1′*Z*,1*S*,2*R*)-2-(hex-1′-en-1′-yl)-1-[[(10″-tetrahydropyranyl)oxy]decyl]cyclopropane **20** (550 mg, 1.51 mmol), hydrazine hydrate (1.2 mL), ethanoic acid (0.2 mL) and satd aq. copper sulfate (0.2 mL) and isopropanol (100 mL). The reaction was stirred for 1 day before being quenched with 10% aq. ammonium chloride solution (30 mL). The mixture was extracted with dichloromethane (2×50 mL), washed with water (2×20 mL) and dried. The organic phase was reduced in vacuo and the residue purified by flash chromatography, eluting with petrol:ethyl acetate (8:1), to yield **21** (480 mg, 87%) as an oil. IR (film) 3056, 2967, 2895, 1432, 109 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.21 (m, OCHO, 1H), 3.28 (t, CH_2, 2H, J 7.9 Hz), 3.08 (m, CH_2, 2H), 1.51 (m, 2×CH_2, 4H), 1.23 (m, C_3H_6, 6H), 1.01 (m, C_8H_{16}, C_4H_8, 24H), 0.61

(t, CH_3, 3H, J 5.6 Hz), 0.34 (m, 3×CH, 3H), –0.42 (m, CH, 1H); ^{13}C NMR ($CDCl_3$): δ 102.4 (OCO), 71.2 (COTHP), 63.1 (COC), 32.8, 31.9, 30.2, 29.7, 29.6, 29.5, 28.7, 26.2, 25.7, 22.7, 15.8, 14.3, 10.9; EI MS m/z 366.3492 (M^+); $[\alpha]_D^{24} = +12.8$ (c 2.35, $CHCl_3$).

4.17. (1*S*,2*R*)-1-Butyroyloxymethyl-2-hydroxymethyl-cyclopropane 22

A solution of 2,2,2-trifluoroethyl butyrate in isopropyl ether was prepared as follows. 2,2,2-Trifluoroethanol (25 g, 0.25 mol) was dissolved in isopropyl ether (IPE) (260 mL) and butyric anhydride (46 mL, 0.29 mol) was added. The mixture was stirred at 4°C and trimethylsilyl trifluoromethane sulfonate (1.0 mL) was added. An exothermic reaction occurred and the temperature rose to 23°C. The solution was stirred at rt for 90 min. GC showed the presence of the required ester plus butyric acid. A solution of sodium hydroxide (10.0 g, 0.25 mol) in water (200 mL) was added, followed by sodium bicarbonate (10 g). The mixture was stirred for 10 min. The aqueous phase was extracted with IPE (35 mL). The combined IPE phases were washed with satd aq. sodium chloride (200 mL) and dried. It was estimated that the IPE solution contained 38.3 g (0.225 mol) of 2,2,2-trifluoroethyl butyrate, assuming a 90% yield of ester. GC showed the complete absence of butyric acid and only two peaks corresponding to IPE and 2,2,2-trifluoroethyl butyrate.

cis-Cyclopropane-1,2-dimethanol[20] (13.0 g, 0.127 mol) was dissolved in tetrahydrofuran (60 mL). The above IPE solution of 2,2,2-trifluoroethyl butyrate (38.3 g, 0.225 mol) was added to pig liver esterase (12 g). The mixture was stirred at ambient temperature and samples withdrawn at intervals. After 48 h, the diol content was low and the mixture was filtered through a pad of Celite, washed well with IPE and the solvent evaporated to yield a yellow liquid (28.7 g). The residue was dissolved in dichloromethane (200 mL) and washed with satd aq. sodium bicarbonate (30 mL), dried and evaporated. Chromatography on silica gel, eluting with petrol: diethyl ether (5:2), gave **22** as a pale yellow liquid (17.85 g, 81%). IR (film) 3428, 1731 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.44 (1H, dd, J 5.6, 11.8 Hz), 3.81–3.72 (2H, m), 3.4 (1H, dd, J 8.9, 11.9 Hz), 2.9 (1H, br, s), 2.3 (2H, t, J 7.3 Hz), 1.63 (2H, st, J 7.4 Hz), 1.3 (2H, m), 0.93 (3H, t, J 7.4 Hz), 0.83 (1H, dt, J 5.1, 8.4 Hz), 0.21 (1H, br, dd, J 5.4, 10.9 Hz; ^{13}C NMR ($CDCl_3$) δ 173.6, 64.3, 62.3, 36.1, 18.45, 18.3, 14.3, 13.5, 7.64; $[\alpha]_D^{24} = -18.1$ (c 1.4, $CHCl_3$).

4.18. (1*S*,2*R*)-1-Butyryloxymethyl-2-formylcyclopropane 23

Pyridinium chlorochromate (PCC) (12.0 g, 27.9 mmol) and anhydrous sodium acetate (1.5 g) were stirred in dichloromethane (65 mL) under an argon at ambient temperature. A solution of (1*S*, 2*R*)-1-butyroyloxymethyl-2-hydroxymethyl cyclopropane **22** (4.8 g, 27.9 mmol) in dichloromethane (25 mL) was added dropwise and the mixture stirred for 3.5 h, when TLC analysis showed that no alcohol remained. Diethyl ether (150 mL) was added together with Celite (10 g). The mixture was filtered through a pad of silica gel and washed several times with diethyl ether. Evaporation of the solvent yielded a slightly yellow oil **23** (4.18 g, 88%), which was stored under argon at –10°C. IR (film) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.4 (1H, d, J 4.42 Hz), 4.45 (1H, dd, J 6.1, 12.0 Hz), 3.88 (1H, dd, J 9.15, 12 Hz), 2.21 (2H, t, J 7.3 Hz), 2.02 (1H, m), 1.99–1.71 (1H, m), 1.68–1.5 (2H, sext, J 7.3 Hz), 1.33–1.1 (2H, m), 0.87 (3H, t, J 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 200, 173.4, 62.2, 36, 26.6, 22.43, 20.38, 18.36, 13.56, 12.72; $[\alpha]_D^{24} = -66.0$ (c 1.45, $CHCl_3$).

4.19. *Z*- and *E*-(1*S*,2*R*)-1-Butyryloxymethyl-2-(hex-1′-en-1′-yl)cyclopropanes 24

A suspension of *n*-pentyltriphenylphosphonium bromide (16.5 g, 39.9 mmol) in dry THF (125 mL) was cooled to –80°C, whilst being stirred under argon. Potassium *t*-butoxide (4.5 g, 40 mmol) in THF (20 mL) was added dropwise until the colour became yellow. The mixture was allowed to warm to rt and the orange/red solution was cooled to –78°C, when (1*S*,2*R*)-1-butryoyloxymethyl-2-formylcyclopropane **23** (3.41 g, 20 mmol) in THF (15 mL) was added dropwise by syringe. The mixture was allowed to warm to rt and stirred for 1 h. The yellow mixture was cooled to –40°C and satd aq. ammonium chloride (40 mL) was added slowly, the colour turning white. The mixture was treated with dichloromethane (60 mL) and 10% aq. ammonium chloride (150 mL). The aqueous phase was extracted with dichloromethane (2×15 mL). The combined organic phases were washed with satd aq. sodium chloride (150 mL) and then dried. The solution was concentrated to a small volume and added dropwise to a vigorously stirred mixture of diethyl ether (40 mL) and petrol (120 mL). Triphenylphosphine oxide separated as a thick gum, some of which solidified. The mixture was stirred for 30 min and the supernatant liquid decanted. The residue was stirred again with diethyl ether (20 mL) and petrol (60 mL), which was again decanted. The combined solutions were filtered through a pad of silica gel (2×5 cm) and evaporated to dryness to yield a solid (5.4 g). This was flash chromatographed, eluting with 10% diethyl ether in petrol to give a mixture (ca. 5:1) of *Z*- and *E*-(1*S*,2*S*)-1-butyryloxymethyl-2-(hex-1′-en-1′-yl)cyclopropanes **24**, as a colourless liquid (3.4 g, 70%) (Found: C, 74.7; H, 11.1. $C_{14}H_{24}O_2$ requires: C, 74.95; H, 10.78). IR (film) 1736 cm^{-1}, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) (major isomer) δ 5.41 (1H, dtd, J 1.2, 7.35, 10.7 Hz), 5.0 (1H, tdd, J 1.53, 9.1, 10.7 Hz), 4.11 (1H, dd, J 7.2, 11.7 Hz), 3.93 (1H, dd, J 8.1, 11.7 Hz), 2.25 (2H, t, J 7.3 Hz), 2.1 (2H, m), 1.73–1.57 (3H, m), 1.4–1.25 (5H, m), 0.91 (1H, dt, J 4.86, 8.3 Hz), 0.9 (6H, t, 2Me, J 7.4 Hz), 0.34 (1H, dd, J 5.5, 10.64 Hz), ^{13}C NMR ($CDCl_3$) δ 173.8, 132.1, 127.4, 65.1, 36.25, 31.7, 27.3, 22.32, 18.48, 16.6, 14.2, 14, 13.65, 12.25; $[\alpha]_D^{24} = +75.9$ (c 1.5, $CHCl_3$). The minor isomer showed in addition δ_H 5.6 (1H, dt, J 15.3, 7.0 Hz) and 5.2 (1H, ddt, J 15.3, 7.8, 1.3 Hz). The spectra were essentially identical to those reported for the separate isomers.[20]

4.20. *Z*- and *E*-(1*S*,2*S*)-2-(hex-1′-en-1′-yl)-1-hydroxymethylcyclopropanes 25

Anhydrous potassium carbonate (7.5 g, 54.4 mmol) was added to *Z*- and *E*-(1*S*,2*S*)-1-butyroyloxymethyl-2-(hex-1′-en-1′-yl)cyclopropanes **24** (4.48 g, 20 mmol) in methanol (75 mL) and the mixture was stirred at rt; after 2.75 h the saponification was complete by TLC. The mixture was filtered through a pad of Celite and evaporated to yield a white solid. This was partitioned between dichloromethane (75 mL) and water (75 mL). The aqueous phase was re-extracted with dichloromethane (2×10 mL). The combined organic phases were washed with brine (75 mL), dried and evaporated to give a mixture (ca. 5:1) of *Z*- and *E*-(1*S*,2*S*)-1-hydroxymethyl-2-(hex-1′-en-1′-yl)cyclopropanes **25** (3.04 g, 98%) as a slightly yellow oil. IR (film) 3353 cm^{-1}; ^1H NMR ($CDCl_3$) (major isomer) δ 5.47 (1H, ddt, *J* 1.2, 7.31, 10.75 Hz), 5.1 (1H, tdd, *J* 1.50, 9.5, 10.7 Hz), 3.75 (1H, dd, *J* 6.5, 11.7 Hz), 3.47 (1H, dd, *J* 8.77, 11.7 Hz), 2.16 (2H, br, q, *J* 7.1 Hz), 1.75 (1H, m), 1.65 (1H, br, s), 1.43–1.25 (5H, m), 1.0 (1H, dt, *J* 4.76, 8.2 Hz), 0.9 (3H, t, *J* 6.8 Hz), 0.37 (1H, dd, *J* 5.36, 10.54 Hz) (the minor isomer showed in addition δ_H 5.6 (1H, dt, *J* 15.3, 7.0 Hz) and 5.2 (1H, ddt, *J* 15.3, 7.8, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 132, 127.76, 63.6, 31.7, 27.2, 22.3, 20.6, 13.85, 13.76, 12.23; EI MS *m*/*z*; $[\alpha]_D^{24} = +86.7$ (*c* 1.2, $CHCl_3$).

4.21. (1*S*,2*R*)-2-Hexyl-1-hydroxymethylcyclopropane 26

To (1*S*,2*S*)-2-(hex-1′-en-1′-yl)-1-hydroxymethylcyclopropanes **25** (3.04 g, 19.7 mmol) in isopropanol (110 mL) was added hydrazine hydrate (60 mL), acetic acid (0.5 mL) and satd aq. copper sulfate (1 mL). The mixture was stirred and heated to 50°C and a hot solution of sodium periodate (2 g) in water (6 mL) was added dropwise. An exothermic reaction occurred and nitrogen was evolved. Ten further 2 g portions of sodium periodate in water (6 mL) were added over approximately 2.5 h, maintaining the temperature in the range 55–70°C. The mixture was stirred at ambient temperature overnight and then diluted with dichloromethane (100 mL), water (300 mL) and brine solution (200 mL). The aqueous phase was extracted with dichloromethane (3×15 mL). The combined organic phases were washed with water (200 mL), brine (100 mL) and then dried. The solvent was evaporated to leave a reddish brown oil (3.02 g). NMR analysis showed the presence of some un-reduced alkene; the oil was dissolved in isopropanol (75 mL) to which was added hydrazine hydrate (25 mL), acetic acid (1 mL) and satd aq. copper sulfate (1 mL). The reduction was carried out as above adding sodium periodate (10 g) in water (30 mL) over 1.5 h at 55–65°C. The mixture was worked up as before except that the dried dichloromethane solution was passed through a short pad of silica gel. On concentration to dryness, a colourless oil **26** was obtained (2.73 g, 87%) (Found: C, 77.1; H, 13.1. $C_{10}H_{20}O$ requires: C, 76.86; H, 12.89) which showed no trace of the alkene in its NMR spectra. IR (film) 3460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.6 (1H, dd, *J* 7.2, 11.3 Hz), 3.52 (1H, dd, *J* 7.9, 11.3 Hz), 1.48–1.12 (12H, m, including the hydroxyl group), 1.1–1.0 (1H, m), 0.83 (3H, t, *J* 6.9 Hz), 0.65 (1H, dt, *J* 4.5, 8.3 Hz), –0.08 (1H, dd, *J* 5.4, 10.1 Hz); ^{13}C NMR ($CDCl_3$) δ 63.3, 31.84, 30.1, 29.2, 28.55, 22.64, 20.3, 18.1, 16.13, 14.1, 9.46; $[\alpha]_D^{24} = -26.1$ (*c* 1.1, $CHCl_3$). The ^1H and ^{13}C spectra were identical to those published for the enantiomer,[20] and to those obtained for compound **9**.

The optical purities of compounds **9** and **26** were assessed by converting each into a Mosher ester, as follows. (*R*)-(−)-α-Methoxy-α-trifluoromethylphenyl acetic acid chloride (53 mg, 0.2 mmol) was added to a stirred solution of the cyclopropane alcohol (30 mg, 0.19 mmol) and triethylamine (58 mg, 0.57 mmol) in dry diethyl ether (2 mL) under nitrogen at rt. After stirring for 16 h, the products were quenched with satd aq. ammonium chloride (2 mL), extracted with diethyl ether (2×5 mL) and the combined organic layers washed with brine (2 mL), water (2 mL), dried and evaporated to give a pale yellow oil (50 mg). The ^1H NMR spectra of the two crude products were quite different in the region δ 4.53–4.12. The product from the (1*R*,2*S*)-isomer **9** showed two one-proton double doublets at δ 4.46 and 4.24; the corresponding signals for the product from the enantiomer **26** were at 4.50 and 4.16. In each case, small signals corresponding to the second isomer were present, but in each case the e.e. was >95%.

4.22. (1*S*,2*R*)-1-Formyl-2-hexylcyclopropane 27

Pyridinium chlorochromate (5.7 g,13.3 mmol), anhydrous sodium acetate (1 g) and 4 Å molecular sieves (2 g) were stirred in dichloromethane (40 mL) under argon at ambient temperature. A solution of (1*S*,2*R*)-2-hexyl-1-hydroxymethylcyclopropane **26** (1.95 g, 12.5 mmol) in dichloromethane (15 mL) was added dropwise and the mixture stirred at ambient for 3 h, when TLC showed no trace of the alcohol. Diethyl ether (80 mL) was added, the mixture stirred for 10 min and then filtered through a pad of Celite. The solution, which still contained some chromium salts, was diluted with petrol (20 mL) and passed through a short column of silica gel (1.5×5 cm) which was washed thoroughly with diethyl ether. The combined filtrates were evaporated to give a light yellow oil **27** (1.82 g, 94%). IR (film) 3059, 2989, 2924, 1700, 1410; cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.4 (d, CHO, 1H, *J* 5.6 Hz), 1.82 (m, CH, 1H, *J* 8.1 Hz), 1.60–1.12 (m, CH, CH_2, C_5H_{10}, 14H), 0.89 (t, CH_3, 3H); ^{13}C NMR ($CDCl_3$) δ 201.9 (CHO), 31.8, 30.0, 29.0, 28.3, 27.9, 22.7, 24.9,14.8, 14.1; EI MS *m*/*z* 155.1440 (M^+); $[\alpha]_D^{24} = -18.6$ (*c* 1.4, $CHCl_3$).

4.23. (1′*Z*,1*S*,2*R*)-2-Hexyl-1-[[(10′-tetrahydropyranyl)-oxy]dec-1′-en-1′-yl]cyclo-propane 28 and (1′*Z*,1*S*,2*R*)-2-hexyl-1-(10′-hydroxydec-1′-en-1′-yl)cyclopropane 29

9-Tetrahydropyranyloxynonyltriphenylphosphonium bromide (13.6 g, 24.0 mmol) was suspended in dry THF

(140 mL), the flask was cooled to −80°C, under argon, and a solution of potassium *t*-butoxide (3.23 g, 28.8 mmol) in THF (30 mL) was slowly added over 30 m with initial manual stirring. After the addition, magnetic stirring became possible and the mixture was allowed to warm to rt and stirred for 1 h, cooled to −80°C and a solution of (1*S*,2*R*)-1-formyl-2-hexylcyclopropane **27** (1.82 g, 11.79 mmol) in THF (30 mL) added. After warming to rt for 1 h, the mixture was cooled to −40°C and satd aq. ammonium chloride (50 mL) was added, followed by dichloromethane (60 mL). Water (300 mL) was added, the organic phase removed and the aqueous phase re-extracted with dichloromethane (2×20 mL). The combined organic phases were washed with 50% aq. brine (200 mL) and dried. On evaporation, a dark brown liquid (12.45 g) was obtained. This was diluted with dichloromethane (5 mL) and added dropwise into a vigorously stirred mixture of diethyl ether (100 mL) and petrol (100 mL). A dark brown oil separated, the supernatant was decanted and the oil stirred again with a 50/50 mixture of diethyl ether and petrol (50 mL). The top layer was again decanted and the combined decanted solutions were dried and evaporated in vacuo. Flash chromatography, using petrol:diethyl ether (5:2) as eluent, gave the (2′*Z*,1*S*,2*R*)-tetrahydropyranyl ether **28** (0.9 g, 21%) and the free (2′*Z*,1*S*,2*R*)-alcohol **29** (0.695 g, 21%). Spectroscopic data for **28** and **29** were essentially the same as for the isomeric compounds **11** and **12**, respectively.

The tetrahydropyranyl ether **28** (0.90 g, 2.47 mmol) was dissolved in a mixture of THF (5 mL) and methanol (10 mL) to which was added water (0.5 mL) and *p*-toluenesulfonic acid (ca. 10 mg). After stirring at rt for 2.5 h, TLC showed the hydrolysis to be proceeding slowly. The reaction mixture was heated under reflux for 1.5 h when TLC showed complete hydrolysis. Saturated aq. sodium chloride (100 mL) and dichloromethane (25 mL) were added. The organic phase was collected and the aqueous phase re-extracted with dichloromethane (2×10 mL). The combined organic phases were washed with 50% brine (50 mL) and dried. Evaporation to dryness gave a yellow oil (0.797 g), which was purified by flash chromatography, eluting with diethyl ether:hexane (1:2), to give the (2′*Z*, 1*S*, 2*R*)-alcohol **29** (0.56 g, 81%) as an almost colourless oil.

4.24. (1*S*,2*R*)-2-Hexyl-1-(10′-hydroxydec-1′-yl)cyclopropane 30

(a) *p*-Toluenesulfonic acid (200 mg) was added to a stirring solution of (1*S*,2*R*)-2-hexyl-1-[[(10′-tetrahydropyranyl)oxy]decyl]cyclopropane **21** (400 mg, 1.09 mmol) in methanol (50 mL). The reaction was stirred at ambient temperature for 18 h when TLC showed no starting material. The mixture was filtered, reduced in vacuo and the residue purified by flash chromatography, using petrol:diethyl ether (2:1), to yield **30** (282 mg, 91%) as a colourless oil. IR (film) 3407, 3045, 2921, 2869, 1262 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.47 (t, CH_2, 2H, *J* 6.5 Hz), 3.01 (brs, OH, 1H), 1.37 (m, 2×CH_2, 4H), 1.19 (brs, $C_{12}H_{24}$, 24H), 0.68 (t, CH_3, 3H), 0.48 (m, 3×CH, 3H), −0.47 (m, CH, 1H); ^{13}C NMR ($CDCl_3$): δ 63.1 (COH), 32.8, 32.0, 31.2, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 28.2, 26.4, 25.2, 22.4, 18.7, 18.5, 15.8, 14.1, 10.9; EI MS *m*/*z* 282.2924 (M^+); $[\alpha]_D^{24}=+14.2$ (*c* 1.52, $CHCl_3$).

(b) Acetic acid (0.5 mL) and satd aq. copper sulfate (0.25 mL) were added to (1′*Z*,1*S*,2*R*)-2-hexyl-1-(10′-hydroxydec-1′-en-1′-yl)cyclopropane **29** (1.08 g, 3.85 mmol) in isopropanol (30 mL) and hydrazine hydrate (15 mL). The mixture was stirred and heated in an oil bath to 60°C. Sodium periodate (5 g) in water (15 mL) was added over a period of 1.5 h while the temperature was maintained at 55 to 66°C, and then at 55°C for a further 1 h. The mixture was diluted with diethyl ether (25 mL), petrol (25 mL), water (75 mL) and brine (50 mL). The aqueous phase was re-extracted with a 1/1 mixture of diethyl ether: petrol (2×50 mL). The combined organic phases were washed with brine (150 mL), dried and evaporated to dryness to yield a pale yellow oil (1.17 g). NMR examination showed some unchanged alkene. The above oil was dissolved in isopropanol (30 mL), hydrazine hydrate (10 mL), acetic acid (0.5 mL) and satd aq. copper sulfate (0.5 mL). As above sodium periodate (4 g) in water (15 mL) was added dropwise to the stirred mixture at 55 to 65°C over a period of 75 min. It was maintained at 55°C for a further 1 h and then worked up as before. This resulted in (1*S*,2*R*)-2-hexyl-1-(10′-hydroxydec-1′-yl)-cyclopropane **30** as a pale yellow oil (1.08 g, 99%) whose NMR spectra showed no trace of alkene and were essentially the same as those in (a), above, and the enantiomer **14**.

4.25. (1*S*,2*R*)-1-(9′-Carboxynon-1′-yl)-2-hexylcyclopropane or (11*S*,12*R*)-lactobacillic acid enantiomer 2

Pyridinium dichromate (124 mg, 1.1 mmol) was added to a stirring solution of (1*S*,2*R*)-2-hexyl-1-(10′-hydroxydec-1′-yl)cyclopropane **30** (260 mg, 0.92 mmol) dissolved in DMF (15 mL) and dichloromethane (10 mL). The reaction mixture was stirred for 2 days at ambient temperature before being quenched with water (10 mL) and extracted into dichloromethane (2×30 mL). The combined organic phases were washed with water (3×50 mL), extracted into dichloromethane (2×50 mL) and dried. The solvent was removed in vacuo, and the crude residue purified by flash chromatography, using petrol:diethyl ether (8:1) as eluent, to yield **2** (205 mg, 76%) as a pale yellow oil. IR (film) 3484–3210, 3062, 2990, 2924, 2834, 1678 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.29 (t, CH_2, 2H, *J* 7.3 Hz), 1.63 (m, 2×CH_2, 4H), 1.29–1.04 (m, C_7H_{14}, C_4H_8, 22H), 0.94 (t, CH_3, 3H, *J* 5.6 Hz), 0.62 (m, 3×CH, 3H), −0.28 (q, CH, 1H, *J* 3.7 Hz); ^{13}C NMR ($CDCl_3$): δ 180.2 (COOH), 54.0, 41.4, 31.9, 29.7, 29.6, 19.5, 29.4, 29.3, 26.9, 24.7, 23.5, 22.7, 22.6, 22.3, 15.7, 14.1, 10.9; EI MS *m*/*z* Found 296.2719 (M^+); $[\alpha]_D^{24}=-0.31$ (*c* 3.85, $CHCl_3$).

4.26. Methyl (11*S*,12*R*)-lactobacillate enantiomer

(1*S*,2*R*)-1-Hexyl-2-(10′-hydroxydec-1′-yl)cyclopropane **30** (1.01 g, 3.52 mmol) was dissolved in

dichloromethane (25 mL) and water (25 mL), acetic acid (0.4 mL) and cetrimide (0.2 g) added. The mixture was stirred and cooled to 0 to 4°C in an ice bath, before adding a cold solution of conc. sulfuric acid (0.5 mL) in water (2 mL). The mixture was maintained at the same temperature whilst adding portions of potassium permanganate (1.3 g) over 1 h. The reaction mixture was stirred overnight at ambient temperature. Sodium metabisulfite was added portionwise to the mixture until all the manganese dioxide was in solution. Dilute hydrochloric acid (10 mL) and dichloromethane (25 mL) were added. The organic phase was collected and the aqueous phase re-extracted with dichloromethane (2×10 mL). The combined organic phases were washed with brine (50 mL), dried and evaporated to dryness, to yield the crude (11*S*,12*R*)-enantiomer **2** of lactobacillic acid as an oily off-white solid (1.22 g). Crude lactobacillic acid enantiomer **2** (650 mg, 22.8 mmol) was dissolved in dichloromethane (20 mL) and cooled in ice/water and ethereal diazomethane was added dropwise until a yellow colour persisted. After standing at rt for 15 min, the mixture was evaporated to yield an orange–white oil. Flash chromatography (petrol:ethyl acetate, 5:1) gave methyl (11*S*,12*R*)-lactobacillate enantiomer, as a colourless oil (661 mg, 98%). IR (film)1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (3H, s), 2.3 (2H, t, J 7.4 Hz), 1.63 (2H, m), 1.35–1.15 (24H, m), 6.89 (3H, t, J 6.92 Hz), 0.65–0.52 (3H, m), –0.33 (1H, m); ^{13}C NMR ($CDCl_3$) δ 174.34, 51.4, 34.1, 31.94, 30.2, 29.6, 29.45, 29.34, 29.25, 29.15, 28.7, 24.95, 22.7, 15.75, 14.11, 10.9; EI MS m/z (M^+); $[\alpha]_D^{24} = -0.33$ (c 1.5, $CHCl_3$).

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References

1. Hofmann, K.; Lucas, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4328–4336.
2. Hofmann, K.; Axelrod, J. G. *Arch. Biochem.* **1947**, *14*, 482–491.
3. Hofmann, K.; Lucas, R. A.; Sax, S. M. *J. Biol. Chem.* **1952**, *195*, 473–480.
4. Hofmann, K.; Sax, S. M. *J. Biol. Chem.* **1953**, *205*, 55–62.
5. Hofmann, K.; Tausig, F. *J. Biol. Chem.* **1955**, *213*, 425–439.
6. Hofmann, K.; Marco, G. J.; Jeffrey, G. A. *J. Am. Chem. Soc.* **1958**, *80*, 5717–5721.
7. Hofmann, K.; Jucker, O.; Miller, W. R.; Young, A. C.; Tausig, B. *J. Am. Chem. Soc.* **1954**, *76*, 1799–1806.
8. Hofmann, K.; Orochena, S. F.; Yoho, C. *J. Am. Chem. Soc.* **1957**, *79*, 3608–3614.
9. Tocanne, J. F. *Tetrahedron* **1972**, *28*, 363–369.
10. Buist, P. H.; Pon, R. A. *J. Org. Chem.* **1990**, *55*, 6240–6241.
11. Coxon, G. D.; Knobl, S.; Roberts, E.; Baird, M. S.; Al Dulayymi, J. R.; Besra, G. S.; Brennan, P. J.; Minnikin, D. E. *Tetrahedron Lett.* **1999**, *40*, 6689–6692.
12. Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337–349.
13. Furakawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1966**, *7*, 3353–3354.
14. Nishimura, J.; Kawabata, N.; Furakawa, J. *Tetrahedron* **1969**, *25*, 2647–2659.
15. Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97–103.
16. Zhao, Y.; Yang, T.-F.; Lee, M.; Chun, B. K.; Du, J.; Schinazi, R. F.; Lee, D.; Newton, M. G.; Chu, C. K. *Tetrahedron Lett.* **1994**, *35*, 5405–5408.
17. Hong, J. H.; Chun, B. K.; Chu, C. K. *Tetrahedron Lett.* **1998**, *39*, 225–228.
18. Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1995**, *60*, 5236–5242.
19. Morgan, B.; Oehlschlager, A. C.; Stakes, T. M. *J. Org. Chem.* **1992**, *57*, 3231–3236.
20. Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron* **1991**, *47*, 1215–1230.
21. Hoffman, J. M.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1245–1246.
22. Nishida, S.; Fushimi, K.; Tsuji, T. *J. Chem. Soc., Chem. Commun.* **1973**, 525–526.
23. Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **1998**, *63*, 6128–6131.
24. Nakanishi, K. In *Natural Products Chemistry*; Nakanishi, K., Ed.; Academic Press: New York, 1975; Vol. 2, p. 49.
25. Baldwin, J. E.; Spring, D. R.; Atkinson, C. E.; Lee, V. *Tetrahedron* **1998**, *54*, 13655–13680.
26. Toshima, H.; Maru, K.; Saito, M.; Ichihara, A. *Tetrahedron Lett.* **1999**, *40*, 939–942.
27. Seki, M.; Kayo, A.; Mori, K. *Tetrahedron Lett.* **2001**, *42*, 2357–2360.
28. Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669–1677.
29. Al Dulayymi, J. R.; Baird, M. S.; Roberts, E. *Tetrahedron Lett.* **2000**, *41*, 7107–7110.
30. Huang, C.; Smith, C. V.; Glickman, M. S.; Jacobs, W. R.; Sacchettini, J. C. *J. Biol. Chem.* **2002**, *277*, 11559–11569.