

The synthesis of both enantiomers of lactobacillic acid and mycolic acid analogues.

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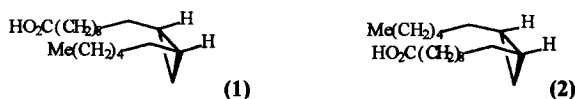
Abstract

(1*R*, 12*S*)-Lactobacillic acid (**1**) has been prepared either from D-mannitol by asymmetric cyclopropanation or from *cis*-cyclopropane-1, 2-dimethanol by enzymatic desymmetrisation. The syntheses of (1*S*, 12*R*)-lactobacillic acid (**2**) and (1*R*, 2*S*) 1-(3'-methoxycarbonylpropyl)-2-octadecylcyclopropane (**26**) and related analogues (**27** and **28**) have also been achieved.

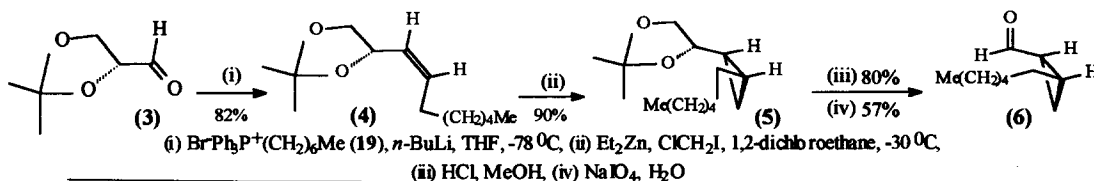
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The cyclopropane ring can be found in a range of naturally occurring compounds including those present in bacterial fatty acids. In 1950, Hofmann and Lucas reported the identification of a new cyclopropane fatty acid as a result of studies on the relation between biotin and fatty acids.^{1,2} Subsequent investigation of *Lactobacillus arabinosus* and *Lactobacillus casei* gave an acid of composition C₁₉H₃₆O₂.^{3,4} Further studies established structure (**1**) with a *cis*-cyclopropane ring at the C₁₁-C₁₂ position;⁵ the absolute configuration has been assigned as 1*R*,12*S*, (**1**), by comparison with related cyclopropyl ketones⁶ and this is reported to have been confirmed.⁷ Surprisingly, there appears to be no synthesis of (**1**) as a single enantiomer. We now describe two routes to (**1**), each involving a common intermediate (**6**), as well as routes to the enantiomer (**2**) and longer chain analogues.

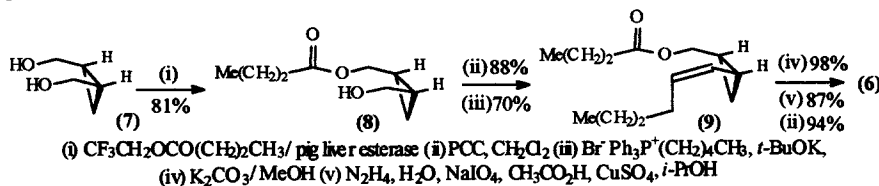


Wittig reaction of the acetonide (**3**), derived from D-mannitol,⁸ with *n*-heptyltriphenyl phosphonium bromide and *n*-BuLi gave the *cis*-alkene (**4**). Cyclopropanation using a modified Simmons-Smith reaction, in which co-ordination of the zinc carbenoid to the neighbouring oxygen atom of the isopropylidene ring of (**4**) delivers the methylene group to the bottom (*re*-*2**si*) face of the alkene,^{9,10} gave (**5**).¹¹ Deprotection of the isopropylidene ring of (**5**) with HCl - MeOH followed by oxidative cleavage of the glycol using aqueous sodium (*meta*) periodate gave (1*R*, 2*S*)-(**6**) ([α]_D²⁴ + 23.6).



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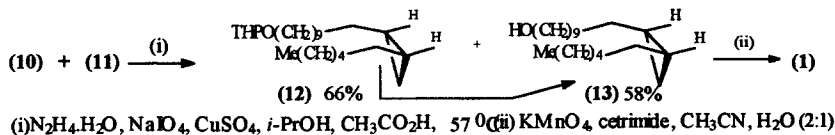
In the second route, the aldehyde (**6**) was prepared from the mono-ester (**8**) ($[\alpha]_D^{24} -17.8$), derived by enzyme catalysed desymmetrisation of *cis*-cyclopropane-1,2-dimethanol (**7**) using 2,2,2-trifluoroethyl butyrate as solvent.¹² Oxidation of (**8**) followed by a Wittig reaction led to (**9**), which was hydrolysed to the alcohol. The double bond was hydrogenated, with di-imide generated *in situ*,¹³ before oxidation to the aldehyde (**6**). The specific rotation of (**6**) was not measured in this instance.



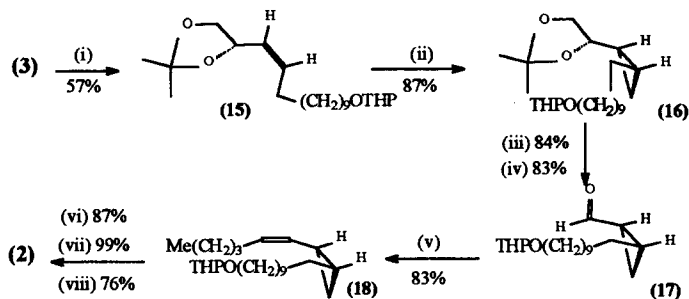
Reaction of (**6**) with the phosphorane derived from 9-tetrahydropyranyloxynon-1-yltriphenylphosphonium bromide led to a mixture of the alkenes (**10**) (11%) and (**11**) (33%):-



Selective double bond reduction was achieved in both cases by treatment of (**10**) and (**11**) with di-imide, as above,¹³ to yield the saturated analogues (**12**) and (**13**), respectively; there was no evidence of hydrogenolysis of the cyclopropane rings. Tetrahydropyranyl deprotection of (**12**) by refluxing for 1.5 h with aqueous-methanolic *p*-toluenesulphonic acid, gave (**13**) (80%). Oxidation of (**13**) with potassium permanganate and cetrimide, in acetonitrile and water, led to (11*R*, 12*S*)-lactobacillic acid (**1**)^{14,15} (62% after conversion into methyl ester).



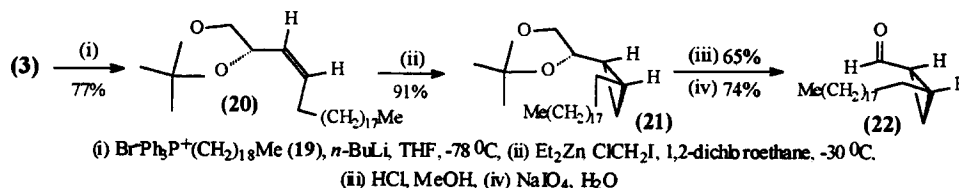
(11*S*, 12*R*)-Lactobacillic acid was also synthesised from the aldehyde (**3**), via the *Z*-alkene (**15**) (57%). Cyclopropanation, as above, gave (**16**)¹⁶ (87%) which, after deprotection of the isopropylidene ring and oxidative cleavage, gave the formyl cyclopropane (**17**).¹⁷



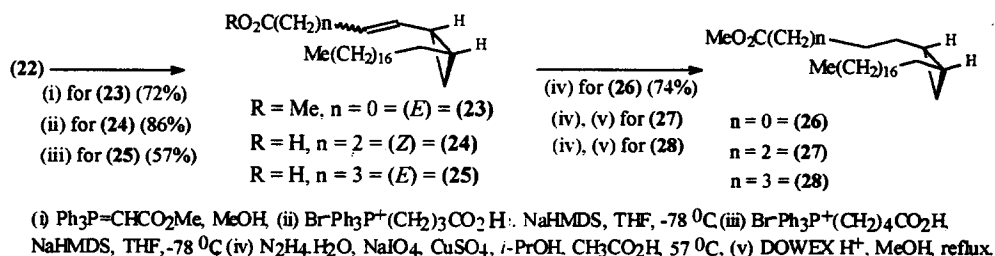
(i) $\text{Br}^-\text{Ph}_3\text{P}^+(\text{CH}_2)_{11}\text{OTHP}$ (**14**), *n*-BuLi, THF, -78°C , (ii) $\text{ClCH}_2\text{I}, \text{Et}_2\text{Zn}, 1,2\text{-dichloroethane}, -30^\circ\text{C}$, (iii) HCl, MeOH , (iv) $\text{NaIO}_4, \text{H}_2\text{O}$, (v) $\text{LHMDS}, \text{Br}^-\text{Ph}_3\text{P}^+(\text{CH}_2)_4\text{Me}, \text{THF}, -78^\circ\text{C}$ (vi) $\text{N}_2\text{H}_4, \text{H}_2\text{O}$, $\text{CuSO}_4, i\text{-PrOH}, \text{CH}_3\text{CO}_2\text{H}, 57^\circ\text{C}$, (vii) *p*TSA, $\text{MeOH}, \text{H}_2\text{O}$, (viii) *PDC*, dichloromethane.

A Wittig reaction of the aldehyde (17) gave the alkene (18) (83%). Selective reduction of the double bond by di-imide,¹³ followed by deprotection of the tetrahydropyranyl ether and oxidation of the alcohol, using PDC in dichloromethane, gave (11*S*, 12*R*)-lactobacillic acid (2) (76%).¹⁸

Long chain 2-alkyl-3-hydroxy "mycolic" acids are major components in the cell walls of *Mycobacterium tuberculosis* and they incorporate *cis* cyclopropane rings of unknown chirality.¹⁹ We describe syntheses of optically pure cyclopropane fatty acids that may be used to probe the chirality of the cyclopropane rings in mycolic acids. Reaction of (3) with nonadecyltriphenylphosphonium bromide (19) and *n*-BuLi in THF at -78 °C gave the *Z*-alkene (20) (77%). Selective cyclopropanation led to the cyclopropane (21),²⁰ which afforded the formyl cyclopropane (22), using standard transformations.



Reaction of (22) with appropriate acid or ester phosphoranes, and necessary bases, yielded the alkenes (23) (72%), (24) (86%) and (25) (57%) which were saturated, using *in situ* generated di-imide, to give the ester (26) $[\alpha]_D^{24} + 34.7$ (74%) and acids which, after esterification, with DOWEX H⁺ in refluxing methanol, afforded the esters (27) $[\alpha]_D^{24} + 7.1$ and (28) $[\alpha]_D^{24} + 1.6$.



Acknowledgements

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11. Compound (5) : $[\alpha]_D^{24} + 19.6$ (c, 0.46 g ml⁻¹, CHCl₃); δ_H 4.10 (q, 1 H, J 4.1 Hz), 3.68 (m, 2 H), 1.39 (s, 3 H), 1.30 (s, 3 H), 1.14 (brs, 9 H), 1.12 (m, 1 H), 0.89 (m, 6 H), 0.18 (m, 1 H); δ_C 108.9, 78.0, 69.5, 32.5, 31.8, 26.8, 25.7, 25.9, 18.1, 15.4, 14.7, 14.0, 10.5, 8.1.
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14. This showed $[\alpha]_D^{24} + 0.16$ or 0.18 (c, 0.55 g ml⁻¹, CHCl₃) (lit.: +0.25)²¹, ν_{max} 3480-3200 (br), 3057, 2988, 2925, 2854, 1653 cm⁻¹, δ_H 2.26 (t, 2 H, J 7.3 Hz), 1.61 (m, 4 H), 1.29-1.04 (m, 22 H), 0.89 (t, 3 H, J 5.6 Hz), 0.56 (m, 3 H), -0.34 (q, 1 H, J 3.8 Hz); δ_C 180.0 (CO), 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.
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16. This showed $[\alpha]_D^{24} + 26.2$ (c, 0.23 g ml⁻¹, CHCl₃), ν_{max} 3059m, 2987m, 2876m, 1410w, 1089s cm⁻¹; δ_H 4.42 (m, 1 H), 3.98 (m, 2 H), 3.39-3.11 (m, CH, 5 H), 3.11 (t, 1 H, J 6.3 Hz), 2.10 (brs, 2 H), 1.26 (m, 6 H), 1.18 (s, 3 H), 1.08 (s, 3 H), 1.06 (m, 16 H), 0.60 (m, 3 H), 0.0 (m, 1 H); δ_C 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.
17. The optical purity of the cyclopropane (17) was confirmed by ¹H NMR after oxidation to the cyclopropane carboxylic acid, which was derivatised with (S)-1-(1-naphthyl)ethylamine via the acid chloride. The enantiomer of (8) ($[\alpha]_D^{24} + 18.5$ (c, 0.50 g ml⁻¹, CHCl₃) was obtained by the enzyme catalysed mono-deprotection of cis-cyclopropane-1,2-dimethanol dibutyrate (Kasel, W.; Hultin, P. G.; Jones, J. B. *J. Chem. Soc., Chem. Comm.* **1985**, 1563; Grandjean, D.; Pale, P.; Guche, J. *Tetrahedron*. 1991, *47*, 1215). By following the method described for (8), this could also be converted into (2).
18. The data for (11S, 12R)-lactobacillic acid (2) corresponded to that of (11R, 12S)-lactobacillic acid (1) except for a specific rotation of $[\alpha]_D^{24} - 0.31$ (c, 3.85 g ml⁻¹, CHCl₃).
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20. This showed $[\alpha]_D^{24} + 6.8$ (c, 0.46 g ml⁻¹, CHCl₃), δ_H 4.07 (br q, 1 H, J 5.2 Hz), 3.61 (m, 2 H), 1.44 (s, 3 H), 1.35 (s, 3 H), 1.25 (s, 32 H), 1.15 (m, 2 H), 0.87 (brt, 3 H, J 6.0 Hz), 0.24 (m, 1 H); δ_C 108.3, 78.2, 69.6, 31.4, 30.7, 29.1, 28.5, 28.3, 27.5, 27.1, 26.9, 26.4, 23.2, 22.7, 17.5, 16.4, 9.8.
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