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

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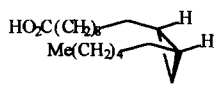
Abstract

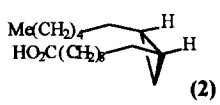
(11*R*, 12*S*)-Lactobacillic acid (**1**) has been prepared either from D-mannitol by asymmetric cyclopropanation or from *cis*-cyclopropane-1, 2-dimethanol by enzymatic desymmetrisation. The syntheses of (11*S* 12*R*)-lactobacillic acid (**2**) and (1*R*, 2*S*) 1-(3'-methoxycarbonylpropyl)-2-octadecylcyclopropane (**26**) and related analogues (**27** and **28**) have also been achieved.

Keywords: Asymmetric cyclopropanation, enzymatic desymmetrisation, chiral cyclopropanes, fatty acids, lactobacillic acid, mycolic acids, Simmons-Smith reaction.

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 $C_{19}H_{36}O_2$ [3,4] Further studies established structure (**1**) with a *cis*-cyclopropane ring at the C_{11}-C_{12} position;[5] the absolute configuration has been assigned as 11*R*,12*S*, (**1**), by comparison with related cyclopropyl ketones[6] and this is reported to have been confirmed.[7] Suprisingly, 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.

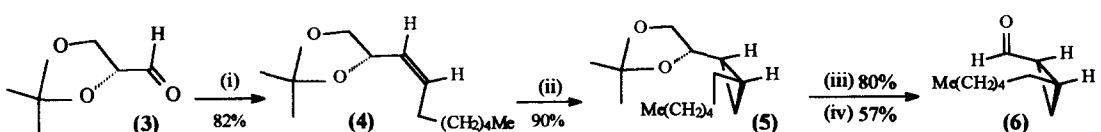


(**1**)



(**2**)

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 (1*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 the glycol using aqueous sodium (*meta*) periodate gave (1*R*, 2*S*)-(**6**) ($[\alpha]_D^{24}$ + 23.6).



(**3**) (**4**) (**5**) (**6**)

(i) $Br^-Ph_3P^+(CH_2)_6Me$ (**19**), *n*-BuLi, THF, -78 °C, (ii) Et_2Zn, $ClCH_2I$, 1,2-dichloroethane, -30 °C, (iii) HCl, MeOH, (iv) $NaIO_4$, H_2O

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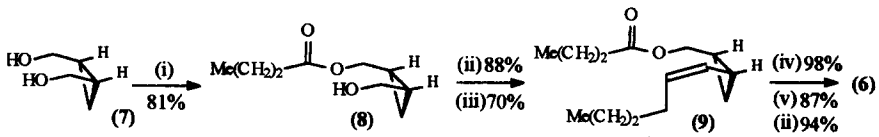
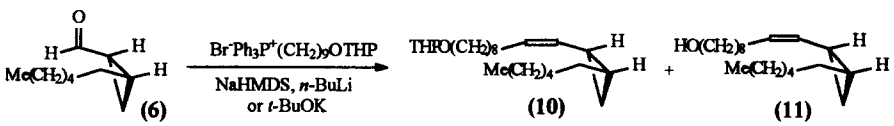
In the second route, the aldehyde **(6)** was prepared from the mono-ester **(8)** ($[\alpha]_D^{24}$ −17.8), derived by enzyme catalysed desymmetrisation of *cis*-cyclopropane-1,2-dimethanol **(7)** using 2,2,2-trifluoroethyl butyrate as solvent.[12] Oxidation of **(8)** followed by a Wittig reaction 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.

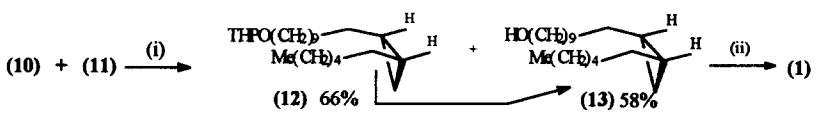


(i) $CF_3CH_2OCO(CH_2)_2CH_3$/ pig liver esterase (ii) PCC, CH_2Cl_2 (iii) $Br^-Ph_3P^+(CH_2)_4CH_3$, *t*-BuOK, (iv) K_2CO_3/ MeOH (v) N_2H_4, H_2O, $NaIO_4$, CH_3CO_2H, $CuSO_4$, *i*-PrOH

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%):-

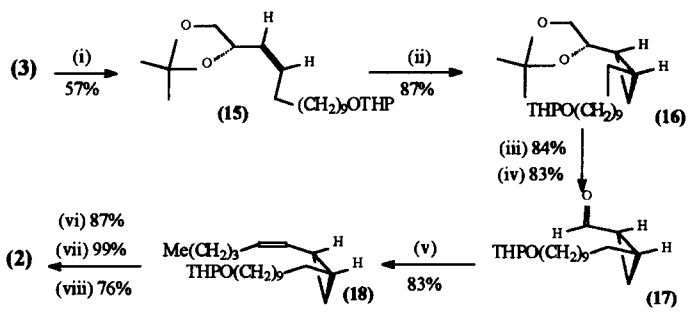


Selective double bond reduction was achieved in both cases by treatment of **(10)** and **(11)** with di-imide, as above,[13] to yield the saturated analogues **(12)** and **(13)**, respectively; there was no evidence of hydrogenolysis of the cyclopropane rings. Tetrahydropyranyl deprotection of **(12)** 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).



(i)$N_2H_4.H_2O$, $NaIO_4$, $CuSO_4$, *i*-PrOH, CH_3CO_2H, 57 °C (ii) $KMnO_4$, cetrimide, CH_3CN, H_2O (2:1)

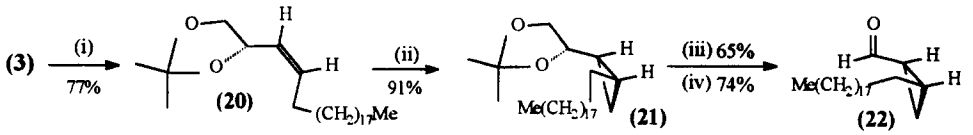
(11*S*, 12*R*)-Lactobacillic acid was also synthesised from the aldehyde **(3)**, via the *Z*-alkene **(15)** (57%). Cyclopropanation, as above, gave **(16)**[16] (87%) which, after deprotection of the isopropylidene ring and oxidative cleavage, gave the formyl cyclopropane **(17)**.[17]



(i) $^-BrPh_3P^+(CH_2)_{11}OTHP$ **(14)**, *n*-BuLi, THF, -78 °C, (ii) $ClCH_2I$, Et_2Zn, 1,2-dichloroethane, -30 °C, (iii) HCl, MeOH, (iv) $NaIO_4$, H_2O, (v) LHMDS, $Br^-Ph_3P^+(CH2)_4Me$, THF, -78 °C (vi) $N_2H_4.H_2O$, $CuSO_4$, *i*-PrOH, CH_3CO_2H, 57 °C, (vii) pTSA, MeOH, H_2O, (viii) PDC, dichloromethane.

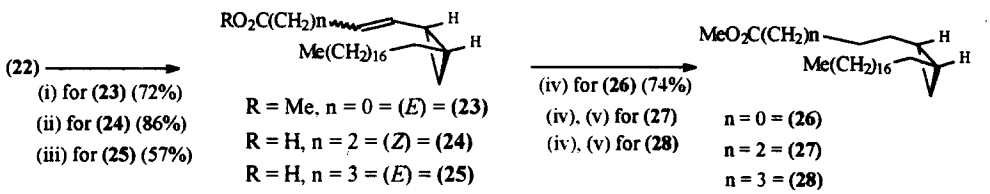
A Wittig reaction of the aldehyde **(17)** gave the alkene **(18)** (83%). Selective reduction of the double bond by di-imide,[13] followed by deprotection of the tetrahydropyranyl ether and oxidation of the alcohol, using PDC in dichloromethane, gave (11*S*, 12*R*)-lactobacillic acid **(2)** (76%).[18]

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 ^{0}C gave the *Z*-alkene **(20)** (77%). Selective cyclopropanation led to the cyclopropane **(21)**,[20] which afforded the formyl cyclopropane **(22)**, using standard transformations.



(i) $Br^-Ph_3P^+(CH_2)_{18}Me$ **(19)**, *n*-BuLi, THF, -78 ^{0}C, (ii) Et_2Zn $ClCH_2I$, 1,2-dichloroethane, -30 ^{0}C, (iii) HCl, MeOH, (iv) $NaIO_4$, H_2O

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.



(i) $Ph_3P{=}CHCO_2Me$, MeOH, (ii) $Br^-Ph_3P^+(CH_2)_3CO_2H$, NaHMDS, THF, -78 ^{0}C, (iii) $Br^-Ph_3P^+(CH_2)_4CO_2H$, NaHMDS, THF, -78 ^{0}C, (iv) $N_2H_4.H_2O$, $NaIO_4$, $CuSO_4$, *i*-PrOH, CH_3CO_2H, 57 ^{0}C, (v) DOWEX H^+, MeOH, reflux.

Acknowledgements

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11. Compound **(5)** : $[\alpha]_D^{24}$ + 19.6 (c, 0.46 g ml^{-1}, $CHCl_3$);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}, $CHCl_3$) (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}, $CHCl_3$), 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}, $CHCl_3$) 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 (11*S*, 12*R*)-lactobacillic acid **(2)** corresponded to that of (11*R*, 12*S*)-lactobacillic acid **(1)** except for a specific rotation of $[\alpha]_D^{24}$ -0.31 (c, 3.85 g ml^{-1}, $CHCl_3$).
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20. This showed $[\alpha]_D^{24}$ + 6.8 (c, 0.46 g ml^{-1}, $CHCl_3$), 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.
21 Nakanishi, K. In *Natural Product Chemistry*, Nakanishi K. Ed.; Academic Press: New York, Vol 2, 1975, 49.