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The synthesis of single enantiomers of a meromycolic acid

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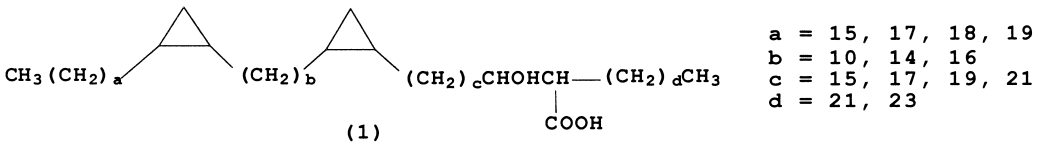
Abstract

3-Oxa-2,4-dioxobicyclo[3.1.0]hexane provides a flexible starting material for the preparation of single enantiomers of a meromycolic acid, a long chain fatty acid containing two remote *cis*-cyclopropanes.

Mycobacterial cell walls show unusually low permeability, a factor which contributes to their resistance to therapeutic reagents. This is believed to be due to an exceptionally thick bi-layer caused by the packing of C_{60}–C_{90} fatty acids (esters).[1] These 'mycolic acids' show an unusual variety of structural features, including *cis*-cyclopropanes (**1**),[2] α-methyl-*trans*-cyclopropanes, α-methyl-β-methoxy and α-methyl-β-keto fragments and variable chain length, as well as a common α-hydroxy-β-alkyl acid functionality.[3,4]



(1)

The balance of these structures, which is dependent on the mycobacterium, changes membrane permeability and fluidity and hence the resistance to a therapeutic agent. Much is now known about the enzymes controlling the biosynthesis of these compounds,[5] and a number of proposals have been made as to the relationship between the different acids and the sequence by which they are produced; an example is the proposal that the *cis*-cyclopropane unit, the α-methyl-*trans*-cyclopropane and the α-methyl-β-alkoxy unit are formed through a common intermediate (Scheme 1).[6] An immediate consequence of such an intermediate would be that the three sub-units might be expected to have a common absolute stereochemistry, at least at the carbon bearing the methyl group and C-1 of the *cis*-cyclopropane.

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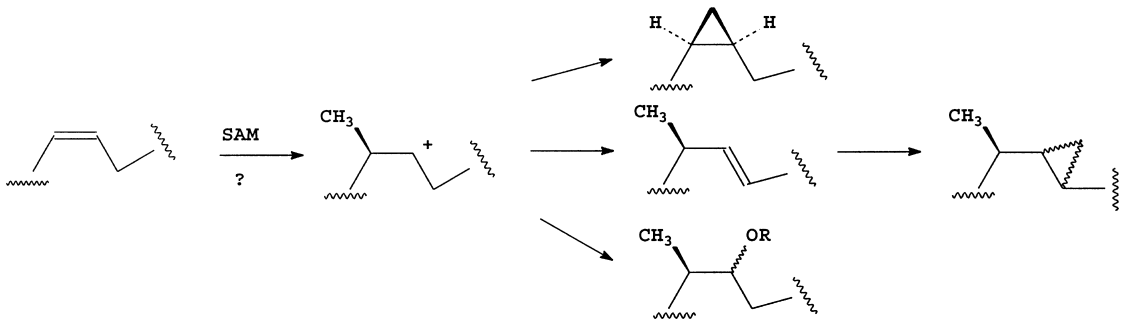
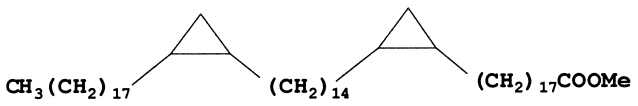


Scheme 1.

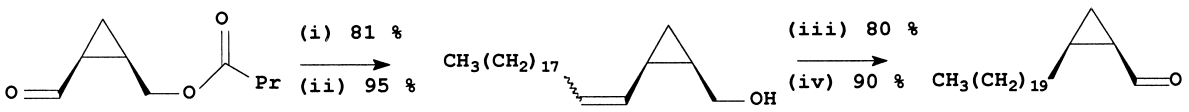
However, very little appears to be known about the absolute stereochemistries of the functional groups present and therefore such comparisons are not possible; even the absolute stereochemistry of the much simpler, but ubiquitous, lactobacillic acid has only very recently been confirmed by synthesis.[7]

Gensler has reported a synthesis of the 'meromycolic acid' (**2**) as a mixture of four stereoisomeric di-*cis*-cyclopropane forms.[8] We now report a route to single enantiomers of such meromycolic acids which can be applied to a variety of chain lengths; the route which proved to be the most effective used a combination of Wittig and Julia reactions.



(2)

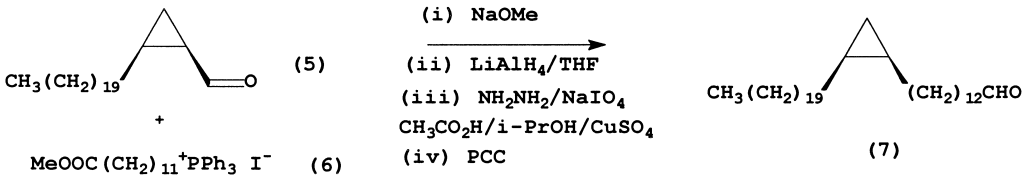
The aldehyde **3** was prepared as described previously from the anhydride of cyclopropane-*cis*-1,2-dicarboxylic acid.[7] A Wittig reaction of this with nonadecyltriphenylphosphonium bromide[9] and *n*-butyl lithium, and reduction with lithium aluminium hydride, led to the alcohol **4** as a mixture of *Z*- and *E*-isomers. Saturation of the alkene with di-imide and oxidation of the alcohol led to aldehyde **5**.



(3) (4) (5)

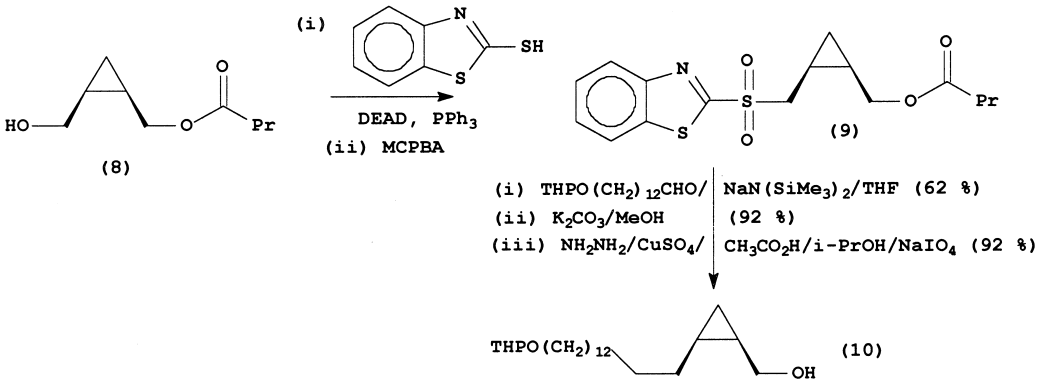
(i) $CH_3(CH_2)_{18}{}^{+}PPh_3Br^{-}$/ BuLi (ii) $LiAlH_4$/THF (iii) $NH_2NH_2/NaIO_4$/ acetic acid/ i-PrOH/$CuSO_4$ (iv) PCC/ CH_2Cl_2

A second Wittig reaction of **5** with the phosphonium salt **6**[10] derived from methyl 12-iodododecanoate, followed by reduction of the ester to the alcohol, saturation of the alkene as before and PCC oxidation, led to the aldehyde **7** ($[\alpha]_D$ –8.2 (*c* 0.166 g/10 ml; $CHCl_3$); 41% overall).



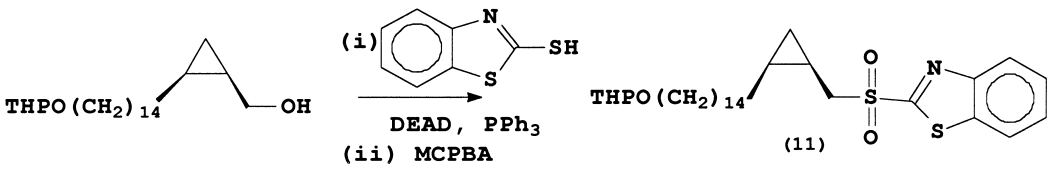
By reversing the sequence of the two Wittig reactions from **3** or by using the enantiomer of **3**,[7,11] aldehyde **7** of opposite absolute stereochemistry could be prepared.

The half ester **8** was converted into the sulphone **9** by reaction with benzthiazole, diethyl azodicarboxylate and triphenylphosphine to give the corresponding sulphide (77%), followed by oxidation with *m*-chloroperbenzoic acid (82%). A Julia reaction of **9** with 13-tetrahydropyranyloxy-tridecanal,[12] base hydrolysis of the butyrate ester and then saturation of the derived mixture of *E*- and *Z*-alkenes (1:1.3) with di-imide as before furnished the second cyclopropane building block **10**.

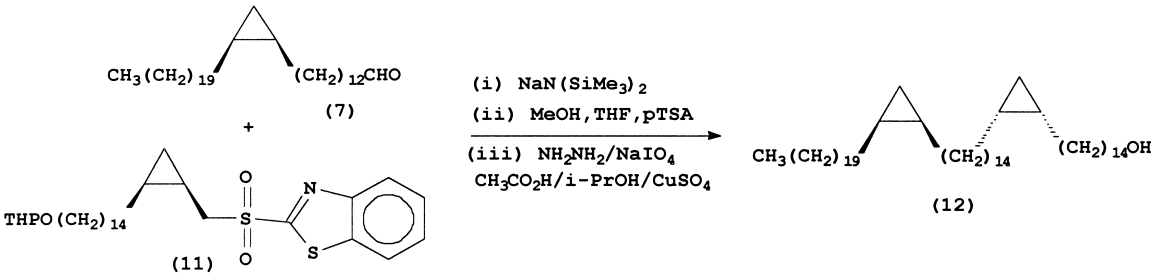


Again, by reversing the sequence of the two Julia reactions, or by manipulating the protecting groups on **10**, the absolute stereochemistry of the second cyclopropane could be reversed.

Compound **10** was further converted into the sulphone **11** (59%) by reaction as before.



In the final sequence, the two cyclopropanes **7** and **11** were coupled to produce the enantiomerically pure alcohol **12** ($[\alpha]_D$ +2.2 (*c* 0.055 g/10 ml; $CHCl_3$)). This is currently being converted into a single enantiomer of hominomycolic acid (**1**). The alcohol **12** was oxidised under phase transfer conditions ($KMnO_4$, CH_2Cl_2, AcOH, H_2O, H_2SO_4, cetrimide) into the corresponding meromycolic acid.



Work is currently under way to convert the alcohol **12** into an intact α-mycolic acid.

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9. Nondecan-1-ol[13] was converted into 1-bromononadecane[14] by reaction with 48% HBr and tetra-*n*-butylammonium bromide and then into the phosphonium salt by refluxing with triphenylphosphine in toluene.
10. Methyl 12-bromododecanoate was converted into the 12-iodo-compound[15] by reaction with sodium iodide in acetone. Reaction of the iodide with triphenylphosphine led to the phosphonium salt **6**.[16]
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12. 10-Iododecan-1-ol tetrahydropyranyl ether[17] was treated with the dianion of propargyl alcohol, and the resultant 13-tetrahydropyranyloxytridec-2-yn-1-ol was hydrogenated and then oxidised to the corresponding aldehyde.
13. See, e.g., Duclos, R. I.; Makriyannis, A. *J. Org. Chem.* **1992**, *57*, 6156; Ucianni, E.; Bonfaud, A.; Lai, R.; Naudel, M. *Bull. Soc. Chim. Fr.* **1969**, 2826.
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