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## A biomimetic approach to the synthesis of a mycolic acid motif

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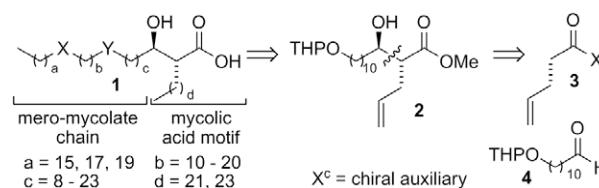
### ABSTRACT

A new method for the stereoselective synthesis of the (*R,R*)- $\beta$ -hydroxy- $\alpha$ -alkyl fatty acid fragment of mycolic acids, via an asymmetric *anti*-aldol reaction is reported. The 'mycolic acid motif' fragment was prepared in three steps and >98% ee.

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Mycolic acids **1** (MAs) are located in the protective wax coat of the cell wall of *Mycobacterium tuberculosis* and other mycobacteria.<sup>1</sup> MAs consist of two main parts, a mycolic acid motif with a 22 or 24 carbon  $\alpha$ -alkyl chain and a  $\beta$ -hydroxy group, and a mero-mycolate chain with variable functional groups.<sup>2</sup> The mycolic acid motif, common to MAs from all mycobacteria, usually has an *R,R* configuration.<sup>3</sup> These complex waxes are recognized by antibodies<sup>4</sup> and therefore show potential for use in TB therapy and new diagnostic techniques such as biosensor assays.<sup>5</sup> Furthermore, they have been shown to re-programme the macrophages to promote a tolerogenic response in experimental asthma and are being explored for their potential in the prevention and treatment of asthma.<sup>6</sup>

Natural mycobacterial MAs are present as complex mixtures containing different functionalities X and Y, and a range of homologues with different chain lengths.<sup>1,2</sup> To fully understand the biological role of MAs there is a need for the synthesis of individual acids with known stereochemistry. In the biosynthesis of mycolic acids, the  $\alpha$  and  $\beta$  carbons are joined in a Claisen-type condensation to give a  $\beta$ -keto product which is selectively reduced.<sup>7</sup> In published syntheses of the mycolic acid motif, two stereocentres are inserted consecutively in three to five steps.<sup>8,9</sup> We now report a more biomimetic approach (Scheme 1) whereby an auxiliary-mediated *anti*-aldol reaction gives the  $\alpha$ -alkyl- $\beta$ -hydroxy product **2** in the required *R,R* configuration in one step. We have adapted the

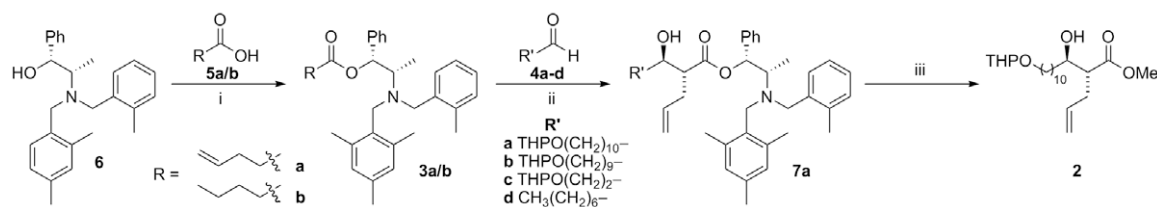


Scheme 1. Mycolic acid structure<sup>1,2</sup> and retrosynthetic analysis.

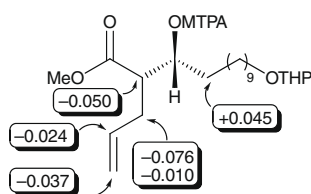
method developed by Kurosu and Lorca,<sup>10</sup> to couple saturated carboxylic acids with short chain aldehydes for the synthesis of **2**, containing a terminal alkene. This can be used to extend the  $\alpha$ -alkyl chain in the mycolic acid motif to its full length of 22 or 24 carbons as described by Toschi and Baird,<sup>9</sup> and can be extended to the full MA by reaction at the THPO-group.<sup>11</sup>

The norephedrine-based auxiliary **6** was attached to both the required unsaturated acid **5a** and a saturated acid **5b** to give chiral esters **3a** and **3b** (Scheme 2). The corresponding zirconium enolates were prepared by treatment with LDA and transmetalation with a zirconium complex (Cp<sub>2</sub>ZrCl<sub>2</sub>). Coupling of these enolates to a variety of aldehydes **4a–d** showed that chain length and functionality in the aldehyde had little effect on the outcome of the reaction, but the introduction of the terminal alkene in the enolate led to lower yields (30–45% for **3a** with **4a–d** vs 50% for **3b** with **4b/d**). Using freshly prepared LDA, strictly anhydrous conditions, a constant temperature of –78 °C (monitored by an internal probe) and dropwise addition of the reagents, the *anti*-aldol product **7a** was obtained from **3a** and **4a** on a 1 g scale in 45% yield with high

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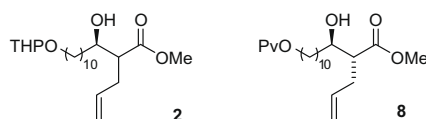


**Scheme 2.** Synthesis of chiral esters **3a** and **3b** and subsequent *anti*-aldol reaction with various aldehydes. Reagents and conditions: (i) EDCI, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (**3a** = 89%, **3b** = 91%); (ii) LDA, Cp<sub>2</sub>ZrCl<sub>2</sub>, THF, -78 °C; (iii) Na(s), MeOH (70%).



**Figure 1.** MTPA ester of compound **2** ( $\Delta\delta_{\text{H}}$  values in ppm).

**Table 1**  
Comparison of the <sup>13</sup>C NMR alkene signals (in ppm) of diastereomers **2** with the literature compound **8**<sup>11</sup>



Carbon	<b>2</b>	<i>epi</i> - <b>2</b>	<i>anti</i> - <b>8</b>
HC=CH <sub>2</sub>	134.9	135.6	134.9
HC=CH <sub>2</sub>	117.1	116.6	117.1

diastereoselectivity (>98%) (determined as described below) after separation from the two *syn*-diastereomers by flash chromatography.<sup>12</sup> The chiral auxiliary was cleaved from aldol product **7a** by transesterification with sodium methoxide, rather than reductively,<sup>10</sup> to yield the methyl ester **2** (70%) (Scheme 2). The configuration of the hydroxy group in **2** was determined using Mosher's method, by conversion into the (*R*)- and (*S*)-MTPA esters.<sup>13</sup> The  $\Delta\delta_{\text{H}}$  values for the protons in the left and right segments (Fig. 1), respectively, indicated an *R* configuration.

On standing in CDCl<sub>3</sub> at room temperature for a week, the solution of **2** partly epimerized at the alpha position giving a mixture of *anti*- and *syn*-diastereomers. A comparison of the <sup>13</sup>C NMR data for the two diastereomers with those published for mycolic acid motif **8**<sup>11</sup> demonstrated that the relative stereochemistry of **2** was *anti* (Table 1).

This synthesis of the mycolic acid motif methyl ester **2** represents a novel approach to a key intermediate that has been used to prepare mycolic acids.<sup>11</sup> The use of *anti*-aldol methodology reduces the number of steps required from six,<sup>11</sup> to two. Prior to the removal of the auxiliary, the diastereomeric products are readily separated giving the desired *R,R*-product in >98% ee. The chiral auxiliary can be recovered and recycled, increasing the atom econ-

omy of the process. By applying the method directly to the aldol reaction of mero-mycolate aldehydes and long chain acids, it is hoped that more efficient syntheses of a range of homologues of natural mycolic acids can be achieved.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.105.

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- Ester **3a** (1.1 g, 2.3 mmol) was added to a solution of freshly prepared LDA (16 mL, 1.0 M) and Cp<sub>2</sub>ZrCl<sub>2</sub> (0.7 mmol) in THF (8 mL) at -78 °C under nitrogen. After 2 h, Cp<sub>2</sub>ZrCl<sub>2</sub> (5.8 mmol) in THF (5 mL) was added and 0.5 h later the aldehyde **4a** (670 mg, 2.6 mmol) in THF (3.5 mL) was added. The mixture was stirred at -78 °C for 2 h, then the reaction was quenched with 1 M HCl. Flash chromatography gave product **7a** in 45% yield.  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3509, 2924, 1722;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>): 7.22–7.06 (7H, m), 6.90 (2H, d, *J* = 7.0 Hz), 6.74 (2H, s), 6.01 (1H, d, *J* = 8.0 Hz), 5.60–5.40 (1H, m), 4.91–4.70 (2H, m), 4.60 (1H, s), 3.90–3.80 (1H, m), 3.75–3.60 (4H, m), 3.54–3.48 (3H, m), 3.44–3.38 (1H, m), 3.37–3.30 (1H, m), 2.65–2.50 (2H, m), 2.49–2.44 (1H, m), 2.26 (3H, s), 2.08 (3H, s), 2.03 (6H, s), 1.80–1.30 (27H, m);  $\delta_{\text{C}}$  (75.4 MHz, CDCl<sub>3</sub>): 174.2, 139.2, 138.5, 137.4, 136.7, 136.2, 134.4, 131.3, 130.9, 130.0, 128.9, 127.8, 126.9, 125.3, 117.2, 98.8, 77.2, 71.5, 67.7, 62.3, 55.5, 50.9, 50.4, 47.3, 35.5, 33.6, 30.8, 29.6, 29.5, 29.3, 26.2, 25.8, 25.5, 22.7, 20.8, 20.0, 19.7, 19.2, 14.1, 9.8; HRMS (+ESI) calcd for C<sub>48</sub>H<sub>70</sub>NO<sub>5</sub> [M+H]<sup>+</sup> = 740.5254, found: 740.5248.
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