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Synthesis of *cis*,*cis*-diunsaturated α-meromycolic acid by a palladium-catalysed alkyl–alkyl Negishi reaction

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ABSTRACT

The first total synthesis of *cis*,*cis*-diunsaturated α-meromycolic acid has been accomplished using a convergent strategy and a palladium-catalysed alkyl–alkyl Negishi reaction as the key step.

Palladium-catalysed cross-coupling reactions between organometallic reagents and organic electrophiles are important transformations in organic synthesis.[1] Nevertheless, despite the fact that the importance of cross-coupling reactions in the synthesis of heterocyclic compounds is indisputable, the applicability of these transformations in the synthesis of lipids has been limited. In particular, alkyl–alkyl cross-coupling reactions of unactivated alkyl halides bearing β-hydrogens are known to be challenging substrates due to their reluctance to undergo oxidative addition and reductive elimination, and their tendency to give β-hydride elimination.[2] Recently, however, progress has been reported in circumventing these difficulties for the Negishi reaction.[3] In this communication, we describe the first synthesis of *cis*,*cis*-diunsaturated α-meromycolic acid (**1**) using a Negishi cross-coupling reaction as the key step (Fig. 1).

The target molecule **1** is an important intermediate in the synthesis of mycolic acids, which are essential components of the cell wall of *Mycobacterium tuberculosis* (*Mtb*),[4] the causative agent of tuberculosis (TB). In *Mtb*, compound **1** is linked to an acyl carrier protein (AcpM) and is the substrate of a cyclopropanating enzyme, PcaA, which has recently been reported as essential for the virulence and persistence of *Mtb*,[5] and thus is considered a promising target in TB drug discovery.[6] Unfortunately, lipid **1** cannot be isolated from bacterial cultures and its total synthesis is of paramount importance to establish a biochemical assay[7] to develop PcaA inhibitors.

During the last 10 years, syntheses of a number of lipids related to mycolic acids have been reported.[8] In these studies, long-chain alkanes have been synthesised by multi-step-procedures that required the formation of a double bond, via Wittig or Julia–Kocienski olefination, followed by its reduction. According to our disconnection strategy for **1** (Fig. 1), we instead envisioned that the framework of the 'proximal' C1–C19 fragment could be synthesised directly by the Negishi coupling of two shorter and easily available fragments. We also decided to synthesise the two *cis* double bonds by two stereoselective Wittig reactions. Specifically, the retrosynthetic analysis depicted in Scheme 1 shows that the proximal double bond of **1** may be synthesised from aldehyde **2** and

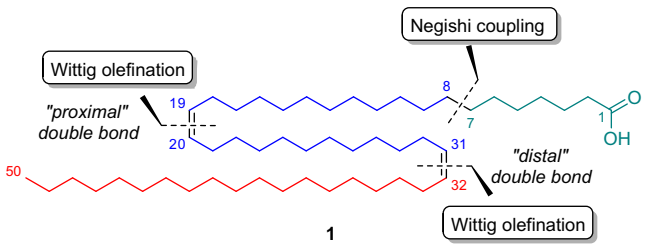

Figure 1. Disconnection strategy for *cis*,*cis*-diunsaturated α-meromycolic acid **1**.

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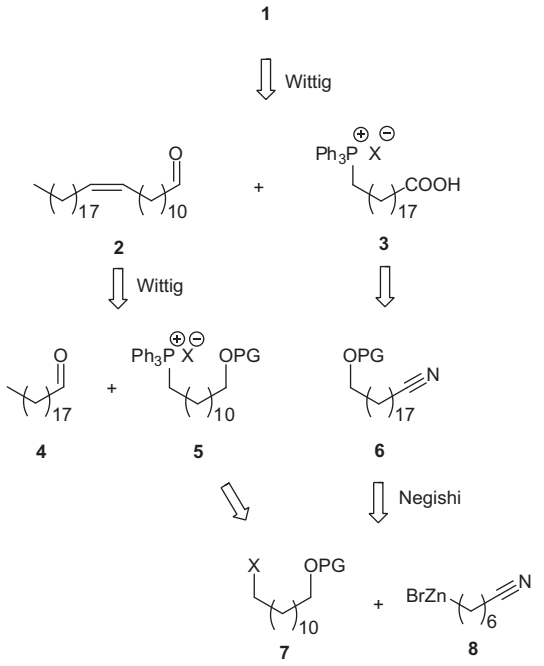
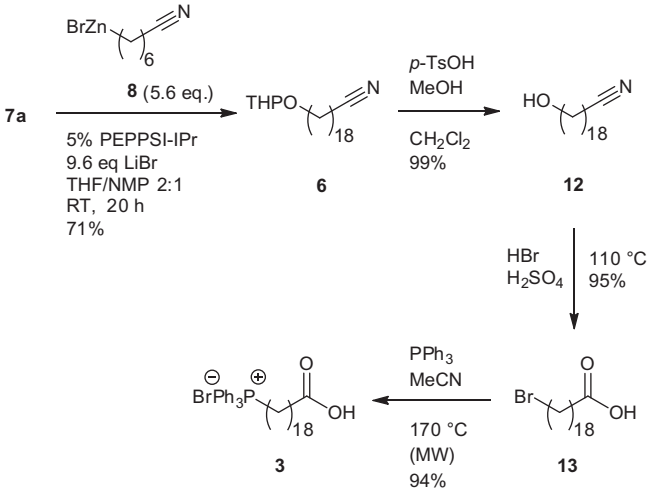


Scheme 1. Retrosynthetic analysis of *cis*,*cis*-diunsaturated α-meromycolic acid **1**.

phosphonium salt **3**, and that the distal double bond may be prepared from aldehyde **4** and phosphonium salt **5**. Interestingly, we envisioned that phosphonium salts **3** and **5** could be obtained from a common organohalide **7**.

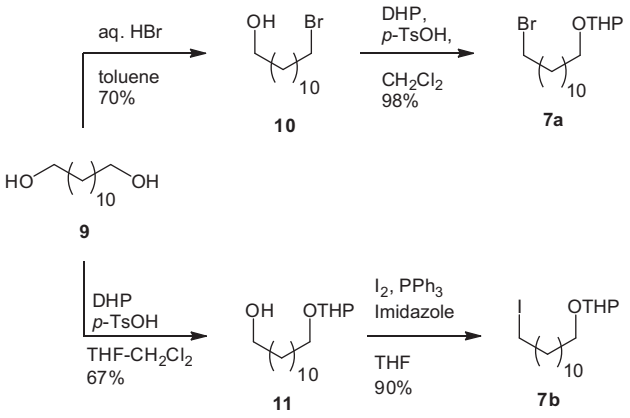
Bromide **7a** and iodide **7b** were readily prepared from 1,12-dodecanediol using a 2-tetrahydropyranyl (THP) group to protect the remaining alcoholic moiety (Scheme 2). The bromination was achieved by treatment with aqueous hydrobromic acid in refluxing toluene, while the iodination was accomplished by treatment with iodine, triphenylphosphine and imidazole in anhydrous THF.[9]

Organohalides **7a** and **7b** were used to synthesise the bifunctionalised C_{19} alkane **6** via a Negishi reaction with alkylzinc bromide **8** using a Pd–*N*-heterocyclic carbene-based precatalyst (PEPPSI-IPr) in the presence of lithium salts.[3,10] However, initial attempts to perform this cross-coupling reaction according to the protocol of Organ et al.[10] yielded **6** in low yields (⩽25%).[11] Under these conditions the starting halides could be recovered in high yields, or unmodified or as corresponding chloride due to LiCl-mediated transhalogenation.[12] Gratifyingly, it was found that bromide **7a** underwent cross-coupling in a 71% yield if the alkylzinc bromide was used in large excess, in the presence of LiBr as the lithium ion source, and with a five-fold higher catalyst loading (Scheme 3). The resulting nitrile **6** was deprotected quantitatively by *p*-toluenesulfonic acid in methanol, and treated with aqueous hydrobromic acid in the presence of sulphuric acid to afford the ω-bromo-carboxylic acid **13** in a 95% yield. Bromide **13** was promptly converted into the corresponding bromide salt **3** in 94% yield by treatment with triphenylphosphine in acetonitrile under microwave irradiation.[13]

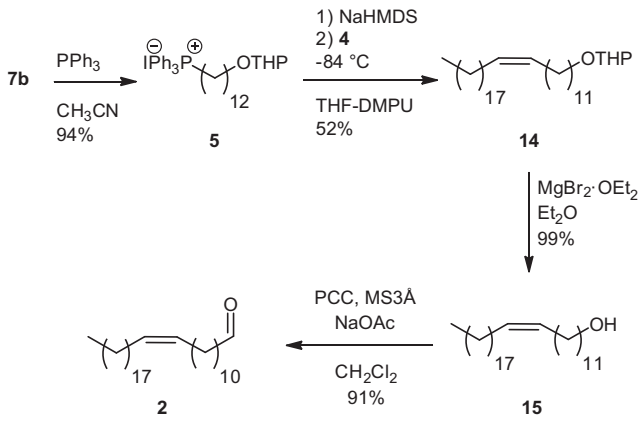


Scheme 3. Synthesis of the phosphonium salt **3**.

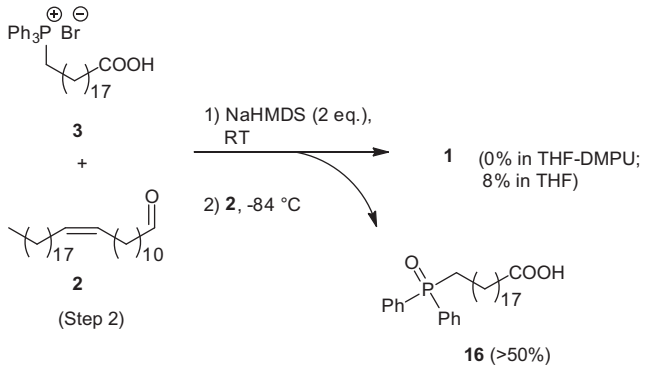
In order to synthesise aldehyde **2** (Scheme 1), nonadecanal (**4**) was efficiently prepared from 1-eicosene via the epoxide intermediate as previously reported,[14] while phosphonium salt **5** was prepared from the halides **7a** or **7b**. However, numerous attempts to treat the bromide **7a** in the presence of triphenylphosphine in toluene, THF or acetonitrile afforded the phosphonium bromide with partial or complete deprotection of the THP group.[15] Conversely, the iodide **7b** was smoothly converted into the desired phosphonium salt **5** using acetonitrile as the solvent (Scheme 4). The resulting phosphonium iodide **5** was treated with an equimolar amount of sodium hexamethyldisilazide to generate the ylide, which underwent stereoselective *cis*-olefination with aldehyde **4** in the presence of DMPU[16] in THF at −84 °C in a 52% yield.[17] Deprotection of THP ether **14** was carried out using magnesium bromide diethyl etherate[18] affording alcohol **15** in a quantitative yield and with conservation of the *Z*-configuration of the existing double bond. Alcohol **15** was converted into the corresponding aldehyde **2** using



Scheme 2. Synthesis of organohalides **7a** and **7b**.



Scheme 4. Synthesis of the aldehyde **2**.



Scheme 5. Synthesis of **1** and unexpected formation of **16**.

PCC under mild conditions in the presence of molecular sieves (MS3Å)[19] and sodium acetate in a 91% yield.

Attempts to carry out the Wittig reaction between phosphonium bromide **3** and aldehyde **2** in THF/DMPU failed to produce the desired compound, leading instead to the formation of diphenylphosphorylalkylcarboxylic acid **16** as major product (Scheme 5). Gratifyingly, omitting the DMPU from the reaction mixture resulted in the synthesis of compound **1** despite the by-product **16** still being present as the major component under these conditions.[20] The conversion of phosphonium salts, containing a long-chain ω-carboxyalkyl group, into the corresponding phosphoryl derivatives has been previously reported to take place in the presence of bases and polar solvents only after several days.[21] Conversely, preliminary results[22] from our studies indicated that this side-reaction is rapid and may be the principal cause of the low yields reported[23] in Wittig reactions of phosphonium salts with pendent carboxy groups. Specifically, we suspect that this base-promoted side-reaction may be due to intramolecular coordination of the carboxylate group on the phosphonium moiety, where DMPU has the role to solvate the sodium ion.

In conclusion, the first synthesis of *cis,cis*-diunsaturated α-meromycolic acid has been accomplished using a convergent strategy using readily available starting materials: 1,12-dodecanediol, 1-eicosene and 6-cyanohexyl zinc bromide. The Negishi cross-coupling reaction has proved to be a useful transformation for the synthesis of long-chain fatty acids. Studies on biochemical applications of compound **1** are in progress and will be published in due course.

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