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Synthesis of 2-*C*-methylerythritols and 2-*C*-methylthreitols via enantiodivergent Sharpless dihydroxylation of trisubstituted olefins

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ABSTRACT

The mevalonate-independent pathway (MIP) is an interesting avenue for antimicrobial lead discovery. Here, we present a unified enantioselective synthesis of all four stereoisomers of 2-*C*-methyltetrol. These are useful building blocks of many bioactive natural products, including 2-*C*-methylerythritol phosphate (MEP) of the MIP biosynthetic pathway.

The identification of novel ways to selectively target invading parasites or microbes within animal hosts is critical to the development of new drug leads and diagnostic probes. In our efforts to develop natural product based leads and imaging agents,[1] we began searching for biosynthetic differences between animal cell types and microbial types. Our search soon led us to the mevalonate-independent pathway (MIP) that exists in Gram-negative bacteria, plant chloroplasts and algae, but not in animals (Fig. 1).[2–4] Indeed, a precedent already exists to support the MIP pathway as a promising avenue to develop drugs against bacteria (e.g., *Mycobacterium tuberculosis*) and malaria.[4,5] Fosmidomycin, an inhibitor of 1-deoxy-D-xylulose-5-phosphate (DXP), is being evaluated in phase II clinical trials to treat malaria, in combination with the antibiotic clindamycin, by Jomaa Pharma GmbH and the medicines for the malaria venture.[6]

2-*C*-Methylerythritol phosphate (**2**, MEP) has been proposed to be a key intermediate in this pathway (Fig. 1) to generate isopentenyl phosphate (IP) by the reductive-migratory isomerism of DXP, a condensation product between pyruvate (Pyr) and glyceraldehyde-3-phosphate (G3P).[4] Herein, we report a unified five-step approach to synthesize all the stereoisomers of 2-*C*-methylerythreitol (**1**) and 2-*C*-methylthreitol (**9**) of MEP (**2**) in good to high enantiomeric purity (80–98% ee). To this end, the Sharpless asymmetric dihydroxylation (SAD) of PMB-O-protected trisubstituted alkenoates was found to be a convenient enantiodivergent tactic.

It should be noted that 2-*C*-methylerythritol (**1**) and 2-*C*-methylthreitol (**9**) have previously been prepared in moderate to good enantiomeric excesses.[7–9] A chemo-enzymatic synthesis of all four isomers has been developed[10] and the natural 2-*C*-methyl-D-erythritol enantiomer [(+)-**1**] has also been prepared using chiral pool starting materials.[11,12] Despite these reported syntheses, we decided to pursue a unified stratagem to all four isomers from readily available, non-chiral hydroxyacetone **3** (Scheme 1).

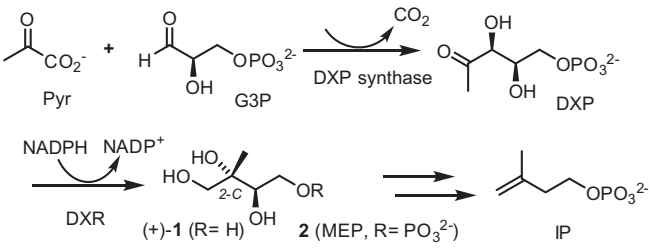

Figure 1. Mevalonate-independent pathway (MIP) via phosphorylated tetraol **1**.

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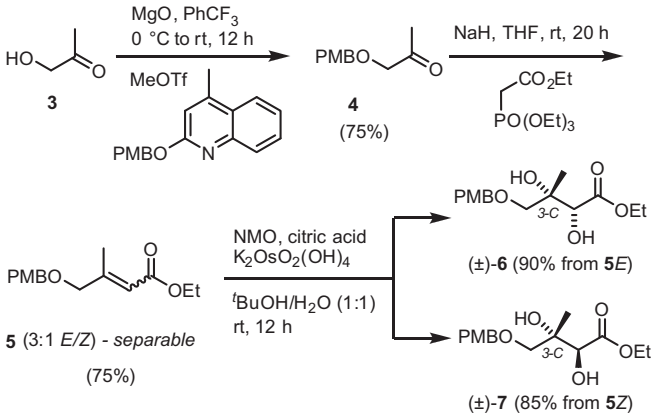
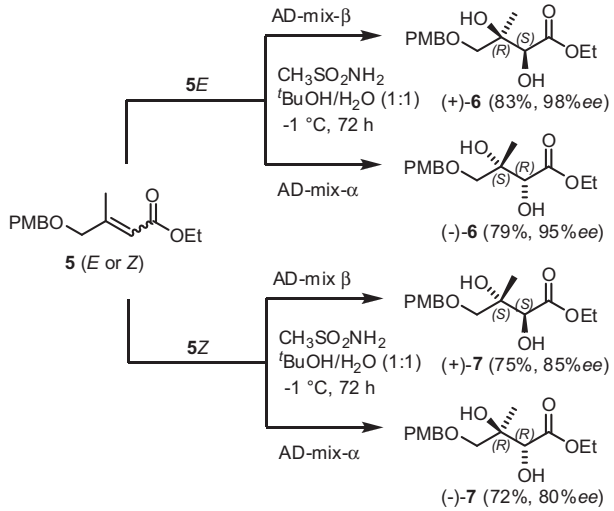


Scheme 1. Stereodivergent synthesis of *thero* and *erythro* esters.

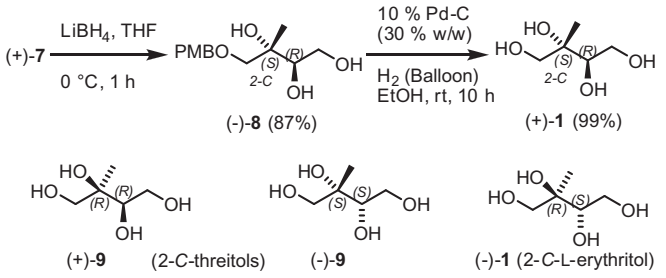
To aid mechanistically in a subsequent SAD step,[13] we began by protecting **3** with a suitable benzyl group. This was surprisingly difficult to achieve in practice; for example, only moderate yields (below 40%) were achieved under standard conditions with freshly prepared benzyl-2,2,2-trichloroacetimidate. Eventually, we settled for the *p*-methoxybenzyl (PMB) ether **4**, whereby the use of Dudley's reagent[14] gave a consistently good yield, and Horner–Wadsworth–Emmons olefination with triethyl phosphonoacetate gave the α,β-unsaturated ethyl ester **5** as a readily separable 3:1 *E*/*Z* mixture.

The pure geometric isomers **5***Z* and **5***E* were confirmed by nOe NMR studies. For reference purposes (i.e., future % ee determination using chiral HPLC) and to check the reactivity of the olefins **5**, we synthesized the racemic diols (±)-**6** and (±)-**7** under Sharpless' modified procedure with citric acid to increase the reaction rate.[15] As anticipated, dihydroxylation of the *cis*-olefin **5***Z* was found to be slower as compared to the *trans*-olefin **5***E*.

Next, we studied the proposed enantiodivergent SAD route to all *threo* **6** and *erythro* **7** *C*-methyldiols by the choice of either AD-mix-α or -β (Scheme 2). Here, we found both the PMB and ethyl ester groups to be essential for optimal enantiomeric excesses for such trisubstituted olefins **5**. The substrate **5***E* under AD-mix-β conditions gave 98% ee of the *threo*-diol (+)-**6**. This is a significant improvement over the reported 82% ee for a benzyl-ether, methyl-ester analogue of **5***E*.[8] A similarly high % ee of (−)-**6** was also



Scheme 2. Catalytic enantiodivergent syntheses of **6** and **7**.



Scheme 3. Synthesis of all dephosphorylated steroisomes **1** and **9** of MEP.

obtained with the use of AD-mix-α (95% ee). Not unexpectedly, the enantioselectivities and reaction rates to produce (+)-**7** and (−)-**7** were lower for the *cis*-olefin **5***Z* as compared to **5***E*[15]; the 72–75% yields and 80–85% ee values are based on recovered **5***Z* after 72 h.

Finally, to form the natural D-isomer (+)-**1** of MEP, ethyl ester (+)-**7** was reduced with $LiBH_4$ to afford triol (−)-**8** in 87% yield (Scheme 3). Deprotection of the PMB group, however, was found to be problematic under oxidative conditions (e.g., CAN or DDQ) due to the adjacent and multiple hydroxy functionalities. A practical solution to this seemingly simply deprotection step was to perform hydrogenolysis with Pd–C (30% w/w) in ethanol. This allowed the smooth generation and isolation of all the tetraols **1** or **9** in near quantitative yields and high purities.

In closing, three main advancements are worth noting. Firstly, each D- or L-isomer of 2-*C*-methylerythritol (**1**) or 2-*C*-methylthreitol (**9**) can be accessed in good to high enantiomeric purity via a reliable, five-step stereodivergent sequence from readily available hydroxyacetone **3** in 30–40% overall yields. Secondly, the PMB-ether/ethyl ester form of the olefin **5** not only improved the enantioselectivity of the SAD reaction, as compared to a related olefin substrate,[8,13] but also **5** could be synthesized in two steps, as compared to four, by virtue of Dudley's neutral benzylation conditions.[14] Thirdly, the title compounds **1** and **9** are useful building blocks to naturally occurring bioactive molecules, including a saccharinic acid lactone (a plant growth regulator),[16] potassium (2*R*,3*R*)-4-trihydroxy-2-methylbutanoate (for leaf closing)[17] and potassium aeshynomate (for leaf opening).[18] In addition to these points, we anticipate this work will provide opportunities in the exploitation of the MIP pathway and in the design of biosynthetic probes and inhibitors to selectively target microbial or parasitic infections.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.071.

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