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Synthesis of an Electrophilic Keto-Tetraene 15-oxo-Lipoxin A_4 Methyl Ester *via* a MIDA Boronate

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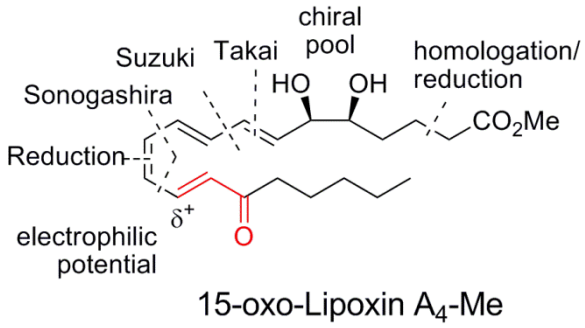

15-oxo-Lipoxin A_4-Me

Graphic Abstract

Abstract: 15-oxo-Lipoxin A_4 (15-oxo- LXA_4) has been identified as a natural metabolite of the fatty acid signaling mediator Lipoxin A_4. Herein, we report a total synthesis of the methyl ester of 15-oxo-LXA_4 to be used in investigations of potential electrophilic bioactivity of this metabolite. The methyl ester of 15-oxo-LXA_4 was synthesized in a convergent 15 step (9 steps longest linear) sequence starting from 1-octyn-3-ol and 2-deoxy-D-ribose with Sonogashira and Suzuki cross-couplings of a MIDA boronate as key steps.

Keywords: eicosanoid, electrophile, palladium-catalyzed coupling, MIDA boronate

Arachidonic acid (AA) plays a key role in cell signaling, as it has been shown to be the biosynthetic source of eicosanoids that mediate the function of leukocytes and other inflammatory responses *via* G-protein-coupled receptor (GPCR) ligand activity. These AA metabolites include prostaglandins, prostacyclins, thromboxanes and leukotrienes.[1] One class of AA-derived mediators termed lipoxins A_4 and B_4 ((5*S*,6*R*,15*S*)-trihydroxy-eicosa-7*E*,9*E*,11*Z*,13*E*-tetraenoic acid and (5*S*,14*R*,15*S*)-trihydroxy-6*E*,8*Z*,10*E*,12*E*-eicosatetraenoic acid, or LXA_4 and LXB_4) are trihydroxytetraenes produced by the successive lipoxygenase oxidations of AA[2] (5-LOX and 12/15-LOX) by stimulated leukocytes. When administered as pure synthetic compounds, these species display pleiotropic actions described[3] as anti-inflammatory and pro-resolving and, because of low concentrations and rapid degradation, are difficult to detect[4, 5] *in vivo*. They, along with the 15(*R*)-stereoisomers[6] (15-*epi*-LXA_4), have been investigated as leads[7] for the treatment[8] of several chronic and acute inflammatory conditions.

In vivo lipoxin A_4 is rapidly metabolized[9] *via* 15-hydroxyprostaglandin dehydrogenase[10] (15-PGDH) oxidation of the 15(*S*)-hydroxy to 15-keto (Fig. 1), followed by reduction of the neighboring C13-14 double bond and finally reduction of the 15-keto to a hydroxyl. While the initial oxidation itself results

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