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SYNTHESIS AND 5-LIPOXYGENASE INHIBITORY ACTIVITY OF 7,7-DIMETHYLEICOSA-5Z,8Z-DIENOIC ACID

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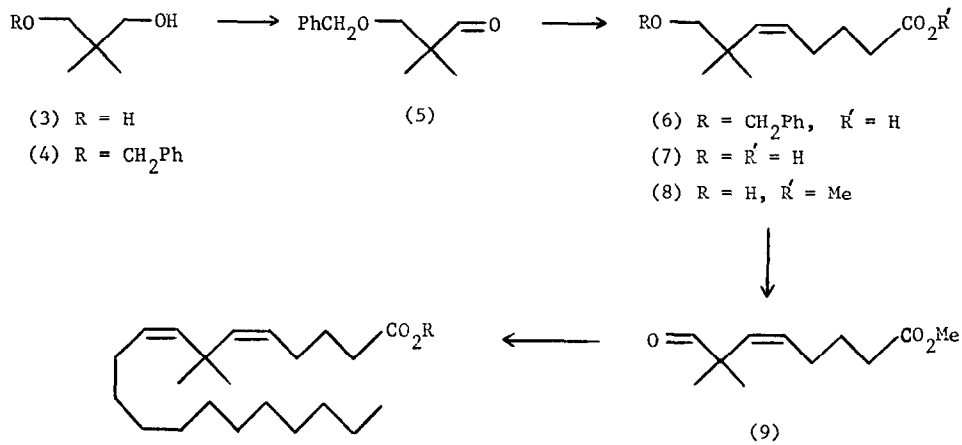
Summary : Synthesis of 7,7-dimethyleicosa-5Z,8Z-dienoic acid and its inhibitory activity against 5-lipoxygenase is described.

We are prompted by recent papers on the 5-lipoxygenase inhibitory activities of eicosapolyenoic acids by Toda et al,[1] and Perchonok et al,[2] to report our findings on the synthesis and inhibitory activities of 7,7-dimethyleicosa-5Z,8Z-dienoic acid (1) and its methyl ester (2). Metabolism of arachidonic acid to leukotrienes is initiated by the abstraction of a hydrogen atom from position 7 of the chain by 5-lipoxygenase. Using similar reasoning to Perchonok et al that a gem-dimethyl group would block this site of attack, we undertook the synthesis of (1). By omitting olefinic linkages at carbons 11-12 and 14-15, it was hoped that (1) would not be in competition with arachidonic acid for binding to the active site of 12-lipoxygenase or cyclooxygenase, and compound (1) would thus be a selective inhibitor of 5-lipoxygenase.

Acid (1) was prepared as follows. Mono protection of 2,2-dimethylpropan-1,3-diol (3) by benzylation[3] gave (4), which was oxidised using pyridinium chlorochromate[4] (PCC) to aldehyde (5) (66%) and then reacted with the ylide formed from (4-carboxybutyl)triphenylphosphonium bromide and potassium t-butoxide[5] to produce 8-benzyloxy-7,7-dimethyloct-5Z-enoic acid (6) (53%) as a pale yellow oil after chromatography. The benzyl group was removed by reaction with sodium in liquid NH_3 to give (7) which was esterified to afford methyl ester (8). Oxidation using PCC yielded aldehyde (9) which reacted with the ylide generated from dodecyltriphenylphosphonium bromide and butyl lithium in THF/HMPT[6] at -78° C to produce methyl 7,7-dimethyleicosa-5Z,8Z-dienoate (2) (61%) purified by chromatography. 7,7-Dimethyleicosa-5Z,8Z-dienoic acid (1)[7] was obtained by hydrolysis of ester (2) with 0.7M potassium hydroxide in aqueous methanol.

Acid (1) at 50 μM inhibited 5-lipoxygenase from RBL-1 cells[8] and human PMN leukocytes[9] by 43% and 26% respectively. Ester (2) was slightly more active, giving inhibitions of 74% and 50% at 50 μM. Both compounds were selective in their action as neither at 50 μM inhibited 12-lipoxygenase from human platelets[10] nor prostaglandin synthetase from bovine seminal vesicle microsomes.[11]



(3) R = H
(4) R = CH_2Ph

(5)

(6) R = CH_2Ph, R' = H
(7) R = R' = H
(8) R = H, R' = Me

(9)

(1) R = H
(2) R = Me

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7 ^{1}HNMR (300MHz) $CDCl_3$: δ 0.84(3H,t,H-20), 1.12(6H,s,2Me), 1.24(18H,br), 1.59(2H,quin, H-3), 1.98(2H,q,H-10), 2.09(2H,q,H-4), 2.3(2H,t,H-2), 5.12(2H,m,H-5,H-9), 5.43(1H,d,J 12Hz) and 5.50(1H,d,J 12Hz) (H-6,H-8).
All new compounds gave satisfactory IR, ^{1}HNMR, and mass spectra.

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11 Another paper recently described the synthesis and the effect on lipoxygenase of 7,7-dimethylarachidonic acid see J.R. Pfister and D.V.K. Murthy, J. Med. Chem., 1983, 26, 1099.

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